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MEDICINE'S CHALLENGE TO THE EDUCATOR*

BY

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An invitation to speak on the problems of medical education in Britain that would be of interest in the United States is one that offers much freedom of choice. Some would choose to display how most of our doctors, particularly the more energetic and talented, are being submerged by uncontrolled growth of committees; and they would discuss how this strange phenomenon has come about, and perhaps how it could be controlled. Others would take the registrar problem, with its temporary interruption in the flow of men through the training posts. Related to this would be the disparity between numbers of permanent posts in the National Health Service and of those being trained to fill them, and the effect of the monopoly created by the National Health Service on recruitment to medicine. Or he might wish to show how the universities can best utilize their new-found freedom to provide a better curriculum, thanks to the new wisdom of the General Medical Council. All these subjects require more study than I have been able to give, and to do justice to each would require a separate essay. Besides, some of these problems, though not the first and the last, are largely administrative, and therefore of restricted interest to our colleagues abroad.

I propose, therefore, to interpret the invitation liberally and to take three issues that affect our attitude to medicine and the teaching of medicine. These three are, firstly, the issue of instruction versus education; secondly, the importance of the proper use of words; and, lastly, the growing importance of population studies in clinical research. I have to confess that these are three old hobby-horses of mine. But I always find the ride exhilarating, and can only hope you may do so too.

Instruction versus Education

My own introduction to the conflict between education and instruction took place during my undergraduate days at Cambridge. One of my friends, who was a teacher of English, pointed out to me that medical students were not being educated: they were being instructed. He explained that education was a training of the mind; that in education a student is set to work in his own time; and the chief function of his teacher is to appraise his efforts, to cure him of bad mental habits, and to encourage him in good ones. He explained to me that this was what was done in the arts faculties of our ancient universities, where a man attended lectures for not more than two hours a day and spent the rest of his time preparing work for his tutor to criticize. The process of instruction, on the other hand, was a process of forced feeding, in which nothing was required of the student except to memorize and to reproduce what he remembered. In such a process the student was required to know the conclusions but not necessarily the evidence on which these were based.

It was clear to me that he was right, and this became even clearer to me in the clinical years, when many teachers did not themselves know what the evidence was or where it could be found. We students were receiving not education but instruction. We went to so many lectures and classes and had so many textbooks to read that we learned things by sheer memory. And we learned the conclusions, not how these had been arrived at. The contrast was all the more striking because between the preclinical and clinical parts of the medical course proper it had been my privilege to take Part II of the Natural Sciences Tripos in Physiology. That was true education under a brilliant collection of teachers—Langley, Barcroft, Adrian, W. B. Hardy, Hopkins, Roughton, Hartridge, Marshall, and others. We had very few lectures, all very much to the point and highly critical, and we were expected to read the more important original papers. I personally owe most to Joseph Barcroft, who not only inspired us in his lectures and practical classes but who also made us write essays for him once a week. There were but four of us. It is not difficult to imagine what a contrast there was between this thrilling intellectual exercise and the dreary grind of instruction of the medical course proper.

My first point is therefore this, that in any branch of university education, including medical education, we should aim at using the methods of education rather than instruction. We must teach the student how to collect the facts, to verify them, to assign a value to them, and how to draw conclusions from them and test those conclusions; in short, how to form a judgment. As Karl Pearson said, "the true aim of the teacher should be to impart an appreciation of method rather than a knowledge of facts," for method is remembered when facts have been forgotten, and method can be used in a new situation where there are no, or too few, facts. The student learns how to learn and can go on acquiring knowledge for the rest of his life.

To obtain some insight into the effect of instruction as opposed to education on a sensitive mind, may I quote Charles Darwin's experiences as a medical student in Edinburgh University in 1825: "The instruction at Edinburgh was altogether by Lectures, and these were intolerably dull, with the exception of those on chemistry by Hope; but to my mind there are no advantages and many disadvantages in lectures compared with reading. Dr. Duncan's lectures on Materia

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Medica at 8 o'clock on a winter's morning are something fearful to remember. Dr. Munro made his lectures on human anatomy as dull, as he was himself, and the subject disgusted me. It has proved one of the greatest evils in my life that I was not urged to practise dissection, for I should soon have got over my disgust; and the practice would have been invaluable for all my future work." In medicine the great difficulty in using the educational approach used to be the small number of teachers and the wide range of subject-matter to be covered. Logistics determined the didactic approach by lectures and large practical classes. This still holds in countries like India, Germany, and elsewhere.

Two Difficulties

In the United States and in Britain two developments have made the educational approach possible—namely, a great increase in staffing of medical schools, and a great development of postgraduate education. The obstacles in our way are now different. They are two. In the first place, knowledge is growing apace. And since man is only one of a very large number of living creatures having many features in common, and since it is believed that ultimately physico-chemical behaviour will be shown to be at the root of all biological behaviour, there is almost no piece of natural knowledge that may not be turned to account in medicine. Our first difficulty is then what limits to set to the fields of knowledge in which to practise the educational method. Our second difficulty is how to teach, whether by lectures, seminars, ward clinics, out-patient clinics, discussion groups, or their variants. My own view is that the ground covered and the precise method used are of less importance than the attitude of mind of the teacher himself.

A true educator must have certain innate characters. He must be intelligent and thoughtful; he must be interested in the material he is using for teaching, and in the minds of those taught. He is more likely to have the right attitude if he has come into close contact himself with a great teacher. Finally, he must be able to detach himself from the ever-increasing pressure of modern life, which tends to crush all individuality from him. Let me quote Fridtjof Nansen, who began life as a zoologist, spent three years of his life drifting across the North Polar ice, one of it with a single companion, and who ended his life as the greatest humanitarian of this century: "The first great thing is to find yourself, and for that you need solitude and contemplation, at least sometimes. I tell you deliverance will not come from the rushing noisy centres of civilization. It will come from the lonely places."

Proper Use of Words

I now come to my second topic, the need for the correct use of language. Of the various points I have to try to make to you I would myself regard this as the most important because the most neglected. The function of language is the transfer of information not only from the mind of one individual to that of another but also, what is often overlooked, to transfer information from one part to another of a single individual's mind. It would seem self-evident that the information that is transferred must be accurate if the action taken is to be closely related to the information received. Electronics, servo-mechanisms, cybernetics, and their amazing products, the automatic machines of great power, versatility, and accuracy; guided missiles; and the like have made us familiar with the importance of transmitting accurate information in order to obtain precise and predictable performance. It is a continuing source of wonder to me that we doctors are so little concerned with the accurate transmission of information within our own minds, and between other minds and ours.

The chief source of inaccuracy in the transfer of information is, I think, the use of technical jargon. On another occasion, in your country, I devoted a little time to the way in which scientists nowadays fence off their subject with technical terms, so that those who have not first learned the language of the specialty cannot understand what the author is trying to say. Those of us who teach and work in the field of cardiovascular diseases are not entirely blameless in this matter. This is, if you like, a manifestation of the growth of nationalism in science, just as the move to teach in Erse, in Welsh, in Afrikaans, and other tongues is one example of the growth of nationalism within the general cultural life of the British Commonwealth. This is important. Nevertheless, I will say no more of it. I want to deal rather with two other aspects—namely, the transfer of information from the mind of the patient to that of the doctor, and from one part of the doctor's mind to another.

In taking a history of the patient's illness I teach my students that they are eliciting an account of the patient's experience. They must use the patient's own words, provided always that both the patient and the doctor are sure that the information conveyed in these words is so far as possible accurate and unequivocal. They must never use terms, like "chesty," which means nothing at all. Nor must they use technical terms, such as anginal pain, or asthma, bronchitis, haemoptysis, or haematemesis, because these are not terms descriptive of experience but are terms that attempt to interpret that experience. Used by the patient, they are often used wrongly, as also indeed they are sometimes by the doctor, who, in using them, prematurely comes to a conclusion. To my mind a good history is one that is expressed entirely in words that are as simple and well known to us as the words used to describe events in the old and new testaments of the Bible. And I suspect we would all agree that a good history is perhaps the most important part of the evidence that takes us to an understanding of our patient's disability.

I always feel I have great difficulty in persuading my colleagues of the importance of what I have just related, but I have even greater difficulty with the next—namely, the errors that we make our own minds commit by the use of technical terms. To illustrate my point I would ask you to consider four examples from cardiovascular and related pathology—namely, shock, arteriosclerosis, bronchospasm, and hypertension.

"Shock"

Shock was a name that came to be used to describe a failure of the circulation, quite distinct from failure of the heart. It became a problem of first importance in the first world war because so many wounded soldiers died presenting this clinical picture. Many distinguished scientists devoted themselves to it, notably Cannon from your side and Bayliss from ours. And the conclusion that emerged from that war was that shock was a traumatic toxaemia produced by the effects of vaso-active substances like histamine released from the injured muscles. It needed the genius of your Dr. Alfred Blalock and the experience of the second world war to show that this was not so, and to show that this clinical picture was not an entity. It was shown that, arising from war wounds, the clinical condition was usually due to loss of blood but could also be due to infection, loss of plasma (as in burns), loss of other body fluids, or due to the vasovagal or fainting attack.

Now, why Cannon, Bayliss, and other distinguished physiologists went wrong was because they were not clinicians familiar with the variety of circumstances in which this clinical picture called shock could arise. They assumed that because the same word was used, therefore the circumstances leading to the final picture were the same; and because in some cases they could exclude the

obvious cause, loss of blood, they assumed that there must be another and more important cause that must operate in all cases. The history of our understanding of traumatic shock is to my mind a most illuminating one. Cannon and Bayliss were most distinguished scientists with a deep insight into the phenomena with which they were dealing. There were few subjects they touched that they did not illuminate. The error came because information was not fully or accurately transmitted in their minds, but was transmitted in the form of a technical term. It is the kind of error that is easily committed where the mind tries to grapple with a problem with which it is not fully and deeply familiar. And too often and to too many of us understanding is limited by the concept consciously or unconsciously conjured up by the technical term to express it.

"Arteriosclerosis"

My second example is arteriosclerosis. As a student this term confused me utterly, and the confusion was worse confounded by its being sometimes used as almost synonymous with hypertension. Cowdrey's book on arteriosclerosis first showed me the light. It became apparent to me that the distinguished authors were equally confused and were talking about different things. In fact, it became apparent that a large number of conditions affecting different coats and different sizes of vessels were there considered, and indeed E. T. Bell said so.

Nowadays our own specialty runs hotfoot to find the reason why increasing numbers of males in the richer countries die young because their coronary arteries become occluded. This is generally described as the problem of atherosclerosis. Now, this term was introduced by Marchand, in a paper given in 1904 to the German Medical Congress, to include both the fatty proliferative nodular change in the intima characteristic of atheroma and the other degenerative, cellular, and calcific changes of intima and media included in the term arteriosclerosis. His paper was indeed entitled "Uber Arteriosclerose." He proposed the term not as an alternative to atheroma, but as an alternative to arteriosclerosis, including lesions of both intima and media, but emphasizing the importance of the intimal fatty change. Atherosclerosis is currently used by most to signify atheroma, which is purely an intimal lesion and is the proper term to describe the coronary lesion that produces ischaemia. Others, however, used it, as it should be used, in Marchand's sense. In fact, I have seen a leading pathologist in this field show a group such as this how atherosclerosis might produce a coronary artery that was wider than normal or one that was narrower. To my rather sceptical eye it seemed that in the first the chief change was in the media, in the second in the intima.

A great deal of wealth and a great deal of man-hours of work are now being invested in this arresting problem. I am tempted to wonder whether the greatest hindrance to our understanding of myocardial infarction lies in the term atherosclerosis. And I wonder if a careful and critical review of the types of arterial change that occur in disease, and their bearing on coronary occlusion, is not the first step that will have to be taken before we reach our goal. As I tried to illustrate by the history of shock, the kind of misconception that technical jargon conjures up is one of the most potent causes, and certainly the most insidious cause, of erroneous conclusion. Many of the distinguished scientists now invading this field of arterial diseases, and particularly ischaemic heart disease, are unfortunately not themselves deeply conversant with the clinical and pathological facts. I often wonder if they really understand what they are seeking to explain, and whether they know how much and how little the term atherosclerosis really means. Or are they being misled as Cannon and Bayliss were by a technical term?

"Bronchospasm"

My third example is bronchospasm. This clearly implies to my mind, and I think to most, that contraction of their muscular walls has greatly narrowed the bronchi. For some years it has been a common practice, even among skilled chest physicians in my country, to describe the association of difficult breathing with rales and rhonchi as bronchospasm. A few years ago I was concerned in a therapeutic trial on the effects of a certain drug on status asthmaticus. As the results came to be set out several of the distinguished doctors wished to refer to the bronchial obstruction that characterizes this state as bronchospasm. This seemed to me to be an intellectual lapse that is characteristic of the age. As every experienced pathologist knows, the characteristic feature of the post-mortem appearances of the lungs in status asthmaticus is the swelling of the bronchial mucosa, and the blocking of the lumen by mucus and other material. To describe this by a term signifying smooth-muscle contraction is surely to reveal a mind that has lost all pretence of being an instrument of precision.

"Hypertension"

My fourth example is hypertension. I will just say this, that the introduction of this technical term, its evolution into the concept of essential hypertension as a disease entity, and the necessity of defining normal blood pressure and hypertension, represent a sequence of events that the readers of Wilfred Trotter's (1941) essays on "The place of general ideas in medicine" and "Has the intellect a function?" will recognize as inevitable. But, as I mentioned earlier, they have made it very difficult for the average doctor to understand the nature of so-called essential hypertension.

Importance of Population Studies in Clinical Research

I would like to leave this rather damaging assessment of a common behaviour of the mind of many who actually lead in medicine to-day and proceed to consider the new importance being given, particularly in Britain, to the study of selected populations with the object of identifying the factors concerned in producing disease and the effects of treatment.

In recent years clinical science has been dominated by what the late Sir James Spence described as phenomenology; that is to say, the application of the methods of physiology and biochemistry to the search for causal sequences in the individual patient. This method has been quite invaluable in showing how the various organs work in disease and what happens when they fail. It has also been invaluable in demonstrating the precise action of drugs which act quickly. Nevertheless, there is no doubt that a great deal of unnecessary effort is put into this form of investigation. I remember the editor of a well-known journal telling me that he had had 53 papers submitted to him in one year on the effects of exercise on the cardiac output in mitral stenosis. Moreover, invaluable as this method is in its proper sphere, it can tell us next to nothing about the genetic and environmental factors producing disease nor how to prevent it or control it. Thus the physiological approach has enabled us to understand the symptoms and signs and electrocardiographic changes in coronary heart disease and assess the effects of vaso-active drugs on exercise tolerance. But it is virtually useless in identifying or measuring the effects of genetic and environmental factors in producing myocardial infarction, or the effects of treatment in preventing recurrence or prolonging life. In other words, the physiological approach is of little value in the prevention or control of disease.

The study of populations to assess the influence of genetic and environmental factors began with Francis Galton, the cousin of Charles Darwin, in his studies in inheritance in man. Galton (1889) found that there were two kinds of inheritance, that of alternative characters such as blue or brown eyes, and that of blended or graded characters such as height. The former type of inheritance was later explained by Mendel's work as representing the effects of single genes, distributed in allelomorphic pairs and behaving as dominants or recessives. The latter type of inheritance is believed to be polygenic—that is, to repre-

sent the sum of many genes, each of which probably behaves in Mendelian fashion. Hamilton, Roberts, Sowry, and I (1954), and Miall and Oldham (1955, 1957) have shown, using extensions of Galton's method, that blood pressure is also inherited as a graded character over the whole range. In the field of cardiovascular disease this method has thus shown that the distinction between so-called normal blood pressure and essential hypertension is nothing else but an artifact and that in the production of levels of blood pressure ordinarily termed essential hypertension genetic factors are important but not exclusive; environmental factors as yet unidentified are probably also concerned.

The aim of this method is to study populations that are alike in every respect except for the variable studied. Because of the complexity of factors concerned and the impossibility of assessing and controlling them all, this means the study of large numbers, with the expectation that the influence of these uncontrolled factors will be the same in the two populations, the differences thus representing the influence of the variable factor. This was achieved by us by measuring blood pressure under the same circumstances in three populations—a sample of the general population, the first-degree relatives of subjects with normal blood pressure, and the first-degree relatives of subjects with so-called essential hypertension. The second essential is to be able to measure a character or to assess the presence or absence of a peculiarity with some precision in the population studied. Finally, there is the mathematical analysis which may need to employ devices for allowing for sex, as Galton had to in his study of height, and allowing for sex and age, as we did in blood pressure. May I just mention an aside here, and say that the most important point is the careful planning of the experiment and collection of data. There is a tendency now to under-emphasize the reliability of the data and their suitability for mathematical treatment. As L. J. Henderson once said of a distinguished colleague, "his mathematical ingenuity is such that he can provide a formula for any set of data, however erroneous."

Much use is being made of the epidemiological method to try to identify the genetic and environmental factors concerned in producing coronary heart disease. There are two major difficulties—namely, the identification of coronary disease with precision in the kind of population samples that need to be compared, and the difficulty of obtaining two populations alike in all respects but one. Thus the higher-income groups in Western countries in which ischaemic heart disease is more prevalent usually differ from the lower-income groups in which the disease is less prevalent in at least four factors: the composition of their diet, their consumption of tobacco, their mental life, and the exercise taken. Nevertheless, I cannot help thinking that a correct choice of groups and a more precise index of prevalence, morbidity, and mortality will ultimately lead to the truth.

Assessing the Effects of Therapy

The other great function of the scientific study of populations is to assess the effects of therapy. The method known in Britain as the controlled therapeutic trial, and developed particularly by Bradford Hill (1951), had its roots in biological assay on the one hand and the testing of chemical manures on the other. Curiously enough, the dominant parent of the controlled clinical trial is the method perfected by R. A. Fisher and his colleagues for the testing of chemical manures, and developed theoretically in Fisher's (1951) "Design of Experiments," for the two methods are used to assess differences in behaviour over weeks, months, and years. Thus development of these two techniques showed how it was possible to measure reasonably accurately the effects produced by altering a single environmental factor, or even two or more environmental factors, despite the variability common to all biological systems.

The principles for such a trial are relatively simple. In the first place, the group of patients for study must be defined as exactly as possible, the reasons for selecting some patients and rejecting others. Secondly, a method must be adopted for allocating about equal numbers of patients at random to the two treatment groups to be compared. Note that allocation of alternate patients to the two groups and allocation by day of admission to hospital are not acceptable, since both give the doctor an opportunity of influencing selection and therefore introducing bias. The two groups selected are then each treated according to the therapies to be compared, by the same doctors in the same institutions, both doctors and patients being, if possible, ignorant of the precise therapy used. The results are finally compared, using objective criteria and eliminating observer error wherever practicable.

I might illustrate the usefulness of the controlled therapeutic trial by contrasting our knowledge of the effects of sympathectomy on the course of hypertensive disease, and the knowledge gained by trial of the anti-tuberculosis drugs. Now, it is an unfortunate fact that, despite the many thousands of patients subjected to sympathectomy by most skilful surgeons, it is still unknown whether this operation affected the prognosis in hypertension, if so how much, and in what groups of patients. Many series of patients were followed and the results analysed and published. But to the best of my knowledge there was not a single series with adequate controls selected at the same time and with the same criteria as the operated group and followed by the same doctors. The control groups were either series such as the well-known one of Keith, Wagener, and Barker at the Mayo Clinic, or patients seen at the same hospital as those selected for surgery but rejected for, or refusing, operation. It is thus quite impossible to judge whether observed differences in mortality were due to treatment or due to initial differences between the groups.

M.R.C. Trial of Anti-tuberculosis Drugs

We may contrast this with the Medical Research Council's therapeutic trial of anti-tuberculosis drugs. The story begins in 1946, when the M.R.C. obtained a small amount of streptomycin to assess its usefulness. Quickly a committee was assembled and a trial arranged (M.R.C., 1948). Six hospitals participated. Patients with acute progressive bilateral tuberculosis of presumably recent origin bacteriologically proved, unsuitable for collapse therapy, aged 15 to 30 years, were selected for study. About one-half (52) were allocated bed rest only, the other half (55) were allocated bed rest and streptomycin. The allocation was made strictly at random. After six months' and one year's treatment the results were compared objectively. At six months in the streptomycin-treated group 69% had improved and 7% were dead, as compared with 33% improved and 27% dead in the control group. At one year the streptomycin-treated group showed improvement in 56% and death in 22%, as compared with improvement in 31% and death in 46% of the controls. By the time this trial had been completed a new anti-tuberculosis drug was available—namely, *para*-aminosalicylic acid (P.A.S.). The Medical Research Council (1950) therefore decided that this should be tried in the same way as streptomycin. The results with P.A.S. seemed less good than with streptomycin, but much the best results were used with the two drugs in combination.

By the time the trial with P.A.S. was completed another anti-tuberculosis remedy had appeared and had passed with great distinction all the preliminary tests. It was isonicotinic acid hydrazide, hereafter referred to as isoniazid. A new trial was therefore planned by the same Medical Research Council Committee, using very much the same methods but with these differences: (1) The scope of the trial was greatly enlarged; no fewer than 39 hospitals collaborated; (2) the variety of cases included was increased. Thus the following criteria were adopted. The sputum must be positive, and the bacilli must not be streptomycin- or P.A.S.-resistant at the beginning of treatment. The patient should not have had more than 15 g. of streptomycin nor 300 g. of P.A.S. during the previous three months. The patient must not be

undergoing collapse therapy. The records from the proposed patients were examined centrally and the cases classified into three main groups and seven subgroups and allocated at random to the two methods of treatment to be compared. (3) Reports of progress were received at one month, two months, three months, and six months from the beginning of the trial.

The speed with which this trial achieved its objective is one of its most impressive features. In February, 1952, preliminary announcements were made in the American press indicating the effects of isoniazid on clinical tuberculosis. The Medical Research Council trial was initiated the same month and treatment begun on March 29, 1952. The preliminary report of the trial was published the same year (M.R.C., 1952), and it established that isoniazid alone was not superior to a combination of streptomycin and P.A.S. During this time 173 patients had been treated with 200 mg. of isoniazid daily, and 158 with 1 g. of streptomycin plus 20 g. of P.A.S. daily. Improvement in general condition was rather better on isoniazid alone, but radiological changes did better on the combination. Acquirement of bacterial resistance to isoniazid was a severe problem, and occurred in 11% of cases at the end of the first month, 52% at the end of the second month, and no less than 71% at the end of the third month. The trial was therefore modified to compare the results of 1 g. of streptomycin daily plus 200 mg. of isoniazid daily with those of streptomycin and P.A.S. It was concluded that the degree of radiographic improvement was essentially the same on streptomycin and isoniazid as on streptomycin and P.A.S., and better in either than on isoniazid alone. Improvement in general condition and conversion of positive to negative culture were more frequent with streptomycin and isoniazid than with streptomycin and P.A.S. Thus it seemed that a combination of streptomycin and isoniazid was in general the most effective treatment known for pulmonary tuberculosis.

In this account I have omitted many details of method and of the knowledge achieved, and I would refer those interested to the article by the late Dr. Marc Daniels (1951), to whose personal qualities so much of this success was due. But I do want to say that I cannot conceive how so much and so exact a knowledge of the relative efficacies of these drugs could have been got so quickly and with so little expenditure of human life and suffering in any other way. Imagine the fate of the tuberculous patients if these drugs had been prescribed without plan or purpose and their assessment left to "clinical judgment." When I reflect on this I am amazed, stupefied, and I confess rather horrified that some of my colleagues, of unquestioned integrity and of no mean intelligence, adopt the attitude they do to controlled therapeutic trials.

I would also like to add that the controlled clinical trial is to my mind the most important new method introduced into clinical science in recent years. It should not only tell us what drugs can do, but if only the practical details can be overcome it could tell us, for example, whether or not overindulgence in fat, or in a particular kind of fat, is a contributing factor in the pathogenesis of ischaemic heart disease. Patients must be treated, and it would seem only sensible that treatment should be designed so that the results shall add to knowledge and help us in the prevention and control of disease, so long as the trial is not against the best interests of the patients.

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SERUM GLUTAMIC OXALACETIC TRANSAMINASE IN ACUTE MYOCARDIAL INFARCTION

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The estimation of glutamic oxalacetic transaminase in serum (S.G.O.T.) as an aid in the diagnosis of acute myocardial infarction was first introduced into clinical practice by LaDue, Wróblewski, and Karmen in 1954. Since then a fairly extensive literature, most of it American, has developed. Particularly comprehensive papers are those of Chinsky *et al.* (1956), Ostrow *et al.* (1956), Kattus *et al.* (1957), and Ratner and Sacks (1957).

The enzyme is widely distributed in the tissues, and high concentrations are present in cardiac and skeletal muscle and in brain, liver, and kidney. It is liberated into the blood on the death of cells of these organs. It is also present in erythrocytes, so that when samples of blood are collected for its estimation, haemolysis must be avoided and the serum or plasma separated as soon as possible. The enzyme will retain its activity for two weeks if the serum is stored at 0–5° C. (LaDue and Wróblewski, 1955). Its concentration can be estimated by the spectrophotometric method of Karmen *et al.* (1955) or by the colorimetric method of Reitman and Frankel (1957).

The level of S.G.O.T. activity in normal controls varies from 5 to 40 units per ml. of serum, with a mean of approximately 21 units (Wróblewski and LaDue, 1955; Kattus *et al.*, 1956). In a normal person the level does not vary by more than 10 units from day to day and is independent of time of day, meals, or previous exercise (Chinsky *et al.*, 1956).

Agress *et al.* (1955) showed that graded experimental infarction in dogs was associated in all cases with increase in S.G.O.T. Infarction of as little as 10%, and possibly less, of the total myocardium produced a significant rise in S.G.O.T. and there was a linear correlation between the peak S.G.O.T. level and the amount of infarction at necropsy. Nydick *et al.* (1957) found that there was no rise in S.G.O.T. in experimental myocardial ischaemia in dogs unless myocardial necrosis had occurred. The rise in S.G.O.T. begins within three hours after infarction, attains a peak in 9 to 23 hours, and returns to normal in three to six days. Agress *et al.* (1956), in other experiments, made the useful observation that if pericarditis was produced by sand, talc, or bacterial infections the S.G.O.T. would rise only if the underlying heart muscle was involved in the injury.

Since the enzyme is widely distributed in the body it was realized early that elevation of S.G.O.T. would occur after necrosis of tissues other than heart muscle. In man a rise in S.G.O.T. has been found after necrotic

lesions of the liver (Wróblewski and LaDue, 1955, 1956; Madsen *et al.*, 1958); of brain (Lieberman *et al.*, 1957), where the peak concentration is attained rather later than in cases of myocardial damage; of skeletal muscle (Merrill *et al.*, 1956); and of the pancreas (Chinsky *et al.*, 1956; Shabetai *et al.*, 1957). A small rise in S.G.O.T. may occasionally occur after pulmonary embolism (Goldstein *et al.*, 1956; Nydick *et al.*, 1957). S.G.O.T. also rises in haemolytic crises (Ostrow *et al.*, 1956) and sometimes with salicylate therapy, but only if the dosage is heavy and prolonged (Manso *et al.*, 1956).

This paper is an account of the part that estimations of S.G.O.T. have to play in the diagnosis and management of acute myocardial infarction.

Material and Method

Observations were made upon 34 episodes of acute myocardial infarction occurring in 28 patients admitted to the Royal Victoria Infirmary, Newcastle upon Tyne. Of these, 18 gave a preceding history of angina of effort. Four patients died, and necropsies were obtained in three. In addition, three patients with status anginosus or acute coronary insufficiency were studied, as well as a few cases of acute cardiac failure with, or without, severe arrhythmias. The cases of myocardial infarction and acute coronary insufficiency were treated with anticoagulants (heparin and phenindione).

Specimens of blood were collected daily for 10 to 14 days, and in some instances for much longer, and examined by one of us (A. J. S.) for the level of S.G.O.T. by the colorimetric method of Reitman and Frankel (1957), using the standardized reagents produced by the Sigma Chemical Company. Estimations were also made of other enzymes, of which an account will be given separately. The erythrocyte sedimentation rate (E.S.R.) was estimated daily by the Westergren method. Twelve-lead electrocardiograms were taken on the day of admission and not less than twice weekly thereafter. In seven cases the electrocardiogram was taken daily.

Estimation of the level of S.G.O.T. in 25 healthy adults gave a range of 10 to 34 units with a mean of 19.0 units (standard deviation ± 6.0 units).

Time of Onset, Height, and Duration of Rise

In many instances the patient was not admitted to hospital early enough for the time of onset of the rise in S.G.O.T. to be gauged, but from observations from those who were and those who had further infarction in hospital, the average time of appearance of an abnormal figure was one and a half days, and the average duration of the abnormal elevation was three and a half days from the onset of pain, with a range of one to six days. These figures agree well with those of other authors—for example, LaDue *et al.* (1954), Denney *et al.* (1956), Chinsky *et al.* (1956), and Ostrow *et al.* (1956), who found that the rise may begin as early as three hours after the onset and that the enzyme returns to normal in one to eight days, most often by the end of the third day.

The peak concentration reached in the uncomplicated cases in the present series varied from 24 to 620 units, with a mean of 194 units—that is, nine times the normal level. Two cases of myocardial infarction with congestive heart failure and centrilobular necrosis of the liver at necropsy had peak levels of 950 and 8,400 units.

Relationship to Body Temperature and E.S.R.

Compared with the fever and the rise in E.S.R., which so commonly follow myocardial infarction, the rise in serum transaminase appeared a full 24 hours sooner. It fell to normal again two days before the temperature and at least a week sooner than the E.S.R. Fig. 1 shows curves from a typical case.

It proved also a more dependable index of infarction, since in only three cases where the blood samples were taken early enough was the S.G.O.T. negative (8.8%). In one-third of the infarcts no rise in temperature took place at all, and even the E.S.R. remained normal in one-fifth. Presumably a larger infarct is needed to raise the E.S.R. than the S.G.O.T. and a still larger one to induce fever.

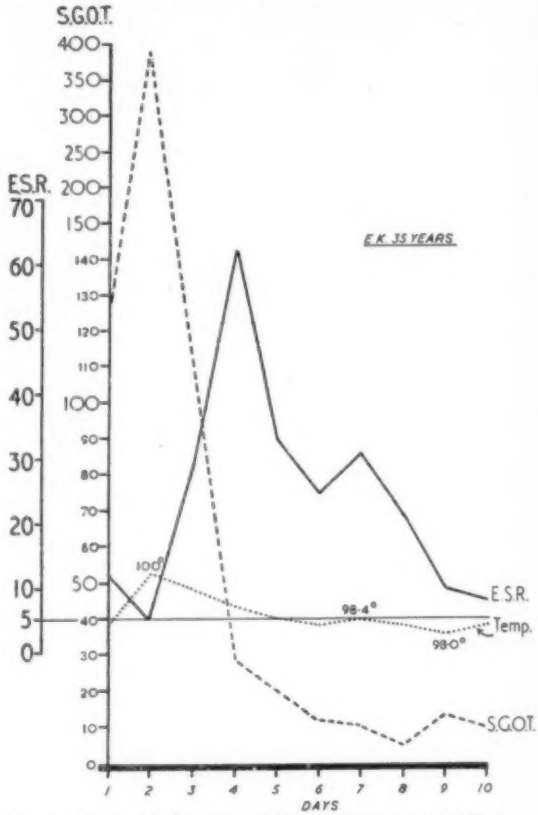

FIG. 1.—Curve showing the relationship between S.G.O.T., temperature, and E.S.R. in a typical case of acute myocardial infarction.

There were in the series several cases where coincidental infections, such as pneumonia, were also responsible for a raised body temperature and E.S.R. as well as a few where the latter was depressed by congestive heart failure. Serum transaminase is unaffected by infections (Ostrow *et al.*, 1956), and, as shown below, rises only in a minority of cases of congestive heart failure. To sum up, the rise in S.G.O.T. is more prompt, more striking, more brief, more sensitive, and more specific than either the body temperature or the E.S.R.

Relationship to the Severity of the Infarct

The size of the infarct has been graded according to the number of leads in which Q wave and T wave changes were detected in the electrocardiogram. In Fig. 2 these have been plotted against the peak levels of S.G.O.T. in the blood of those patients in whom the form of the curve has demonstrated that the peak level had not been missed. It will be seen that there is a linear relationship, although this is a very rough one, not only because the electrocardiographic method of assessing the size of infarct is crude but also because when the S.G.O.T. curves are examined, and are related to the clinical history, a significant number of patients sustain their infarcts in stages over a period of several days. In them, a time-concentration curve would doubtless constitute a much better guide to severity than the single-peak reading, as has already been stressed by Kattus

et al. (1957). Fig. 3 is taken from a good example of such gradual infarction.

Since it has been shown experimentally that an infarct of less than 10% may not produce an elevation of serum transaminase (Agress *et al.*, 1955), it seems likely that in human subjects, too, infarcts may be so small that they do not produce an elevation. This is borne out by experience in the present series, where, on three occasions, pain and electrocardiographic changes in the course of a patient's treatment in hospital suggested that there had been an extension of infarction but no rise of transaminase took place. There was one further and more clear-cut case where the electrocardiogram showed clearly a fresh infarct but the serum transaminase was not elevated. There was also one patient in whom the clinical features were extremely suggestive of fresh myocardial infarction but both electrocardiogram and transaminase remained normal.

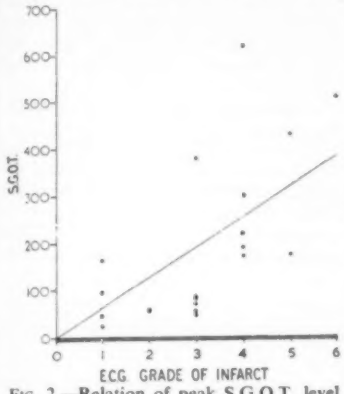

FIG. 2.—Relation of peak S.G.O.T. level and E.C.G. grade of infarct in 20 patients with acute myocardial infarction.

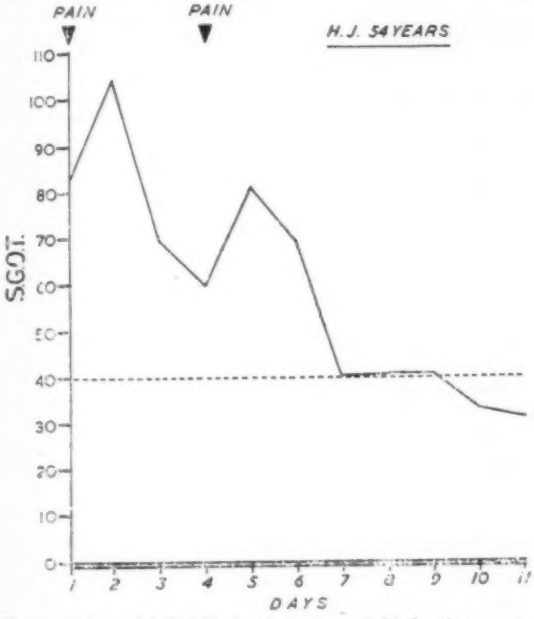

FIG. 3.—Curve of S.G.O.T. showing myocardial infarction occurring in stages over several days.

In some instances, however, the probability is that the elevation of the transaminase above the normal does not attain the arbitrary 40 units which has been set as the upper limit of the normal range. Fig. 4 shows an example where the clinical features and the electrocardiogram strongly suggested a fresh infarct, and the acute rise in serum transaminase is in accord with this even though the maximal elevation is below 40 units.

Cases with Previous Infarction

In nine cases there was a history of previous myocardial infarction, and in five of these, as well as in two others—that is to say, in 21% of the episodes of definite fresh myocardial infarction—the electrocardiogram was so distorted by the previous infarct that on the single initial tracing alone it was impossible to deduce with certainty that fresh infarction had occurred. In these patients the serum transaminase was abnormally high within 48 hours and proved most helpful. Subsequent electrocardiograms confirmed the diagnosis. There is no doubt that in cases of suspected acute myocardial infarction where there is either a history or electrocardiographic evidence of previous infarction the estimation of serum transaminase has its greatest value in establishing that there has been a fresh lesion. Such cases constitute about a quarter of the fresh infarcts seen.

The serum transaminase is also helpful when patients are already under treatment for an acute myocardial infarct and the occurrence of pain, collapse, or other signs suggests that there has been fresh extension of infarction. In such cases the electrocardiogram is often so distorted by the recent necrosis, and perhaps by pericarditis occurring with it, that it is most difficult and often impossible to decide whether

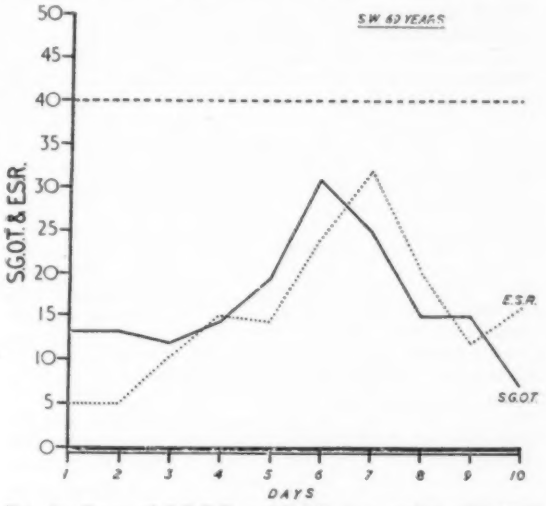

FIG. 4.—Curve of S.G.O.T. and E.S.R. in a patient with acute myocardial infarction, with the peak S.G.O.T. level below 40 units.

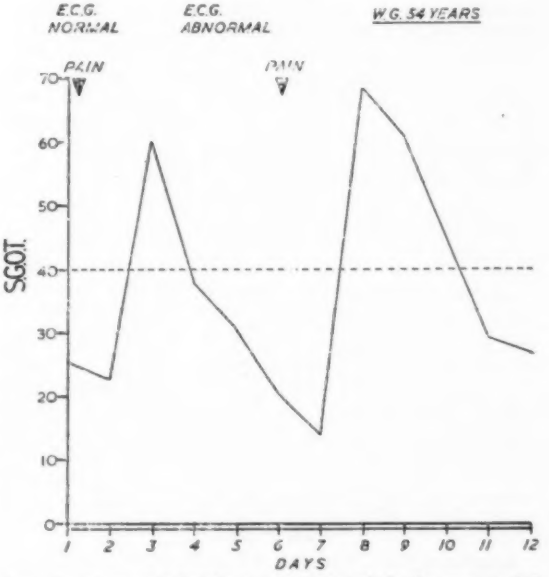

FIG. 5.—Curve of S.G.O.T. in a patient with further myocardial infarction during the course of treatment.

there has been fresh necrosis. It is in these cases that serial estimations of serum transaminase are most likely to be helpful, since they will show the baseline level to which that individual's transaminase falls, and any striking elevation above this closely following upon an attack of pain can be taken as evidence of new damage. Fig. 5 shows such a case.

Other Obscuring Factors in the Electrocardiogram

The diagnosis of myocardial infarction by electrocardiography is less often obscured by arrhythmias, such as the tachycardias and bundle-branch block, by digitalis effects, and by previous left ventricular strain than it is by previous infarction. In the present series there were only two cases in which such factors created serious difficulties compared with five in which previous infarction operated similarly. Nevertheless, the serum transaminase is helpful in this minority, for in both these cases it was normal and the conclusion reached was that there had been no infarction.

Acute Coronary Insufficiency

Other authors (Rudolph *et al.*, 1955; Nydick *et al.*, 1957) have found in experimental narrowing of coronary arteries in animals that unless necrosis is produced in the myocardium a rise of serum transaminase will not be observed, and it has been found in human beings, too, that if the clinical and electrocardiographic picture is solely one of ischaemia without necrosis then the transaminase remains unaltered (Kattus *et al.*, 1956). In the present series there were three such cases of acute coronary insufficiency or status anginosus, all treated with anticoagulants. The usual difficulty in such cases is to distinguish on the electrocardiogram between such ischaemia and limited infarction, often subendocardial. Repetition of the tracings, trying the effects of nitroglycerin upon them, and observing the E.S.R. and body temperature may all help, but sometimes the difficulty remains unresolved. One would expect the serum transaminase to assist in a similarly circumscribed way, for if necrosis is small enough and gradual enough in onset, it would seem likely that no diagnostic curve or level might be observed. Experience of the three cases in this series has borne this out, and has suggested that the enzyme estimation is complementary to, but not necessarily more reliable than, the electrocardiogram in showing whether or not necrosis has taken place.

False Negatives

The S.G.O.T. was elevated in all except three of the cases of definite infarction here described where the blood samples had been taken early enough—that is, false negatives were 8.8%. Denney *et al.* (1956) found false negatives in only 4.75% of definite infarcts, while Kattus *et al.* (1957) had none amongst 111 patients with proved myocardial infarcts, probably because of the frequency with which they took blood samples for analysis. In a review of 264 patients, Ratner and Sacks (1957) had 8% false negatives among 64 patients with definite myocardial infarction, and this will probably prove to be a representative figure in clinical practice, for the S.G.O.T. rise may be very transient, as is shown in Fig. 6, and very frequent sampling is hardly practicable as a routine.

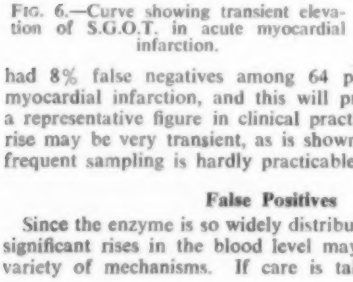

FIG. 6.—Curve showing transient elevation of S.G.O.T. in acute myocardial infarction.

False Positives

Since the enzyme is so widely distributed it is obvious that significant rises in the blood level may be produced by a variety of mechanisms. If care is taken to separate the serum or plasma of the blood sample from the red cells then false elevation due to liberation of the enzyme from haemolysed erythrocytes should not occur. Its liberation into the blood stream from other tissues is a much more important cause of false-positive results. Destruction of red cells in the tissues is one important cause, and particularly so where there has been some tissue destruction as well as haemorrhage; haemorrhagic pancreatitis is a conspicuous example of this. Where the enzyme content of the tissue is low, as in the brain and in the lung, infarction brings only slight rises. When it is high, as in the liver, the elevation consequent upon tissue damage may be enormous. This does not often cause trouble in diagnosis, although one patient, not included in this series, was admitted under the care of one of us (H. A. D.) with the diagnosis of suspected myocardial infarction, and investigation showed that the rise in his transaminase (109 units) was due to subacute alcoholic hepatitis, his heart being clinically and electrocardiographically normal.

It is apparent that serum transaminase is helpful in the differential diagnosis of myocardial infarction only if one is fully aware of the capacity of other tissues to liberate it. Much more important in cardiology is the possibility of the enzyme being liberated in substantial amounts from a liver congested and necrotic from heart failure. The literature about this is scanty. Conrad (1957) mentions DuToit's (1956) report of an elevation in S.G.O.T. in 16 out of 23 patients in uncomplicated cardiac failure. When it does occur the blood level attained may be very high, as in one case in the present series where a young woman of 29 years with acute cor pulmonale due to emphysema and pulmonary infection was found to have a transaminase level of 710 units; nothing in the history or the electrocardiogram suggested that there had been myocardial infarction. Two of DuToit's cases had S.G.O.T. levels of more than 2,000 units, and one of these had advanced central necrosis of the liver at necropsy. It has been said that in cases of liver disease the serum glutamic pyruvic transaminase (S.G.P.T.) is elevated to a greater extent than the S.G.O.T., in contrast to the findings in myocardial necrosis. In the present series this was occasionally true, but exceptions were too numerous for the double estimation to be worth while as a routine test.

Prognosis

It has been said (Chinsky *et al.*, 1956) that a peak level of S.G.O.T. greater than 200 units carries a poor prognosis. However, the peak level may not be observed, either because the patient dies before the maximum is reached or because the patient is admitted on the downstroke of the transaminase curve. In this series two patients died with S.G.O.T. levels of 57 and 70 units, and in both of these the peak was probably missed. There were eight patients with a peak S.G.O.T. level above 200 units and only two died. Both of these, with S.G.O.T. levels of 950 and 8,400 units, had only moderate-sized recent infarcts at necropsy, but there was marked centrilobular necrosis of the liver.

Many factors are involved in the prognosis of acute myocardial infarction, of which the size of the infarct, reflected in the peak level of S.G.O.T., is only one, and this peak level may in any case be further raised if there is acute heart failure with hepatic centrilobular necrosis, and perhaps also if there is acute haemorrhagic pericarditis complicating the picture.

S.G.O.T. in other Cardiac Conditions

Also of interest in cardiology are the affections of the heart other than acute myocardial infarction in which a raised S.G.O.T may be found. The role of pericarditis has already been mentioned. The arrhythmias *per se* do not raise the enzyme level, but may do so in occasional instances, including one case of the present series and one case out of 14 in the series of Chinsky *et al.* (1956), where the extremely rapid heart rate precipitated acute heart failure with presumed centrilobular necrosis of the liver. The same is true of acute pulmonary oedema (Chinsky *et al.*, 1956).

Ostrow *et al.* (1956) quote one case of Fiedler's myocarditis in which the S.G.O.T. was elevated as one would expect, and Chesler (1958) reports elevated levels in diphtheritic myocarditis. Nydick *et al.* (1955a, 1955b) give an interesting account of its elevation in acute rheumatic carditis. The latter at any rate cannot often be confused with myocardial infarction, and no such difficulty arose in the present series.

Summary

Serial daily estimations of serum glutamic oxalacetic transaminase (S.G.O.T.) for at least 10 days have been made in 34 acute episodes of myocardial infarction occurring in 28 patients. The results have been compared with changes in erythrocyte sedimentation rate (E.S.R.), temperature, and electrocardiogram.

Estimations of S.G.O.T. are most useful (*a*) when the electrocardiogram is obscured by previous myocardial infarction, arrhythmias, bundle-branch block, left ventricular strain, and digitalis; (*b*) when extension of myocardial infarction is suspected; and (*c*) to distinguish between acute coronary insufficiency and myocardial infarction.

There was no rise in S.G.O.T. in 8.8% of the cases of fresh myocardial infarction.

The maximum elevation of S.G.O.T. roughly corresponds with the electrocardiographic estimation of the size of the infarct only if other causes of a raised transaminase can be excluded. The most important of these in myocardial infarction is centrilobular necrosis of the liver secondary to cardiac failure.

In small infarctions serial estimations of S.G.O.T. may show a characteristic curve even though the peak does not exceed 40 units.

We thank the following house-physicians, Drs. W. S. B. Cherry, R. Hart, J. M. Kendall, and J. King, for their practical help in this investigation. We are also grateful to Mr. D. P. Hammersley for help with the diagrams, and to Dr. A. Latner for facilities in the department of pathology.

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SERUM TRANSAMINASE: ITS CLINICAL USE IN DIAGNOSIS AND PROGNOSIS

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Human serum contains several enzymes concerned with the reaction of transamination. The one most commonly determined is serum glutamic oxalacetic transaminase (SGO-T), which catalyses the reversible reaction:

$$\alpha\text{-Ketoglutarate} + \text{L-aspartate} \underset{\text{transaminase}}{\rightleftharpoons} \text{glutamate} + \text{oxalacetate}.$$

Similarly serum glutamic pyruvic transaminase (SGP-T) catalyses the reaction:

$$\alpha\text{-Ketoglutarate} + \text{L-alanine} \underset{\text{transaminase}}{\rightleftharpoons} \text{glutamate} + \text{pyruvate}.$$

Cohen and Hekhuis (1941) showed that transaminase was in highest concentration in cardiac and skeletal muscle. LaDue *et al.* (1954) also found it to be present in the brain, liver, and kidney in lower concentrations.

The serum transaminase level (SGO-T) has been found to be elevated following myocardial damage, hepato-cellular necrosis, pancreatitis, trauma to skeletal muscle, myositis (including dermatomyositis), active rheumatic carditis, and any process associated with active damage to skeletal or cardiac muscle (LaDue and Wróblewski, 1955; Wróblewski and LaDue, 1956; Ratner and Sacks, 1957).

The curve of serial serum transaminase estimations would appear to be characteristic in cases of myocardial infarction, and it has been suggested that a characteristic curve occurring within the normal range of values may be found in some cases of angina (Chinsky *et al.*, 1956) or associated with a very small infarct (Ratner and Sacks, 1957). These authors also found that the serum transaminase level remains normal in patients with cerebrovascular damage, acute or chronic infections, acute phlebitis, uraemia, neoplastic, allergic, or metabolic diseases, unless associated with damage to skeletal or heart muscle. Further, there appears to be no apparent correlation with age, sex, colour, weight, leucocyte count, blood sedimentation rate, the presence or absence of fever, heart failure or shock, or the use of anticoagulant drugs or cortisone.

The above evidence suggests that serial transaminase readings are a possible aid to diagnosis in cases of doubtful myocardial infarction and might prove to be related to the actual size of infarct and, because of this, a possible guide to prognosis. We felt, therefore, that a small series of cases investigating these points was justified.

Technique Employed.—The technique we used was that devised by Frankel and Reitman (1957). In this method the amount of keto-acid formed in one hour is determined colorimetrically by the formation of

a highly coloured "hydrazone," using a spectrophotometer or photoelectric absorptiometer in the range 500 to 520 mμ.

Results

Serum transaminase levels were estimated in 31 cases of myocardial infarction and the typical findings in several cases are described below.

(47) *Case 1.*—Woman, aged 69. Angina three weeks; eight hours' central chest pain. Serum transaminase: 24 SGO-T units 8 hours after onset, 156 units at 32 hours, 27 units at 4 days, 18 units at 8 days. E.C.G.: (*a*) posterior infarct eight hours after onset; (*b*) much improved six weeks later.

(21) *Case 2.*—Man, aged 59. Angina two years; eight hours' central chest pain. Serum transaminase: 216 SGO-T units 56 hours after onset, 64 units at 4 days, 54 units at 6 days, 32 units at 7 days. E.C.G.: antero-lateral infarct 80 hours after onset.

(3) *Case 3.*—Man, aged 63. Hypertension; angina one week; four hours' central chest pain. Serum transaminase: 184 SGO-T units 12 hours after onset, 103 units at 36 hours, 49 units at 60 hours. E.C.G.: (*a*) postero-lateral infarct 24 hours after onset; (*b*) unchanged seven days later.

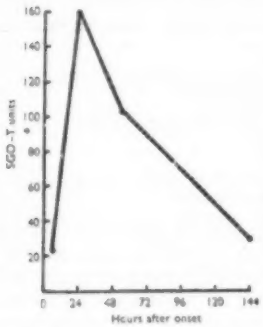

FIG. 1.—Case 4. Serum transaminase readings.

These cases show the typical transiently raised transaminase values in myocardial infarction, the diagnosis in each case being confirmed clinically and on electrocardiography.

(8) *Case 4.*— Man, aged 49. Angina one year; five hours' central chest pain. Serum transaminase: 23 SGO-T units 6 hours after onset, 160 units at 24 hours, 102 units at 54 hours, 30 units at 6 days (Fig. 1). E.C.G.: normal bar Q wave V_{4-7} 48 hours after onset; antero-septal infarct 10 days after onset (Figs. 2 and 3).

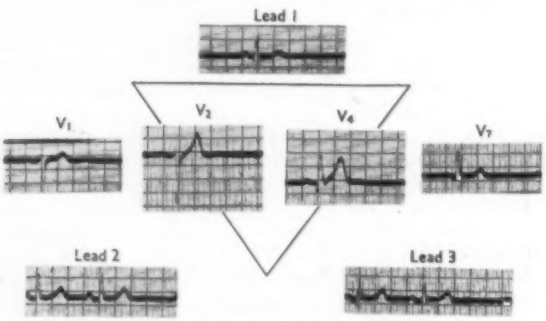

FIG. 2.—Case 4. E.C.G. 48 hours after onset.

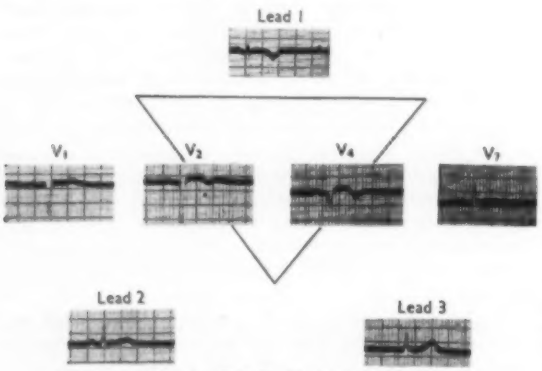

FIG. 3.—Case 4. E.C.G. 10 days after onset.

(44) *Case 5.*—Man, aged 62. Chronic bronchitis; cor pulmonale; jaundice (painless). ? Cardiac cirrhosis. Serum transaminase: 460 SGO-T units day after admission. E.C.G.: left bundle-branch block day of admission. Serum bilirubin, 11.3 mg./100 ml. (total). Necropsy: Enlarged heart; right ventricular hypertrophy; extensive recent septal infarct involving anterior wall of both ventricles; liver showed cardiac cirrhosis.

(17) *Case 6.*—Man, aged 77. Prostatic carcinoma with metastases. Atrial fibrillation. Serum transaminase: 40 SGO-T units 3 days after admission, 30 units at 5 days, 86 units at 6 days, 77 units at 7 days. E.C.G.: auricular fibrillation and right bundle-branch block three days after admission (Fig. 4). Necropsy: Terminal bronchopneumonia; carcinoma of prostate with metastases; recent occlusion of circumflex coronary artery.

(12) *Case 7.*—Man, aged 61. Three days' central chest pain. Serum transaminase: 430 SGO-T units at 4 days after onset, 550 units at 5 days. E.C.G.: left bundle-branch block five days after onset. Died. Necropsy not obtained.

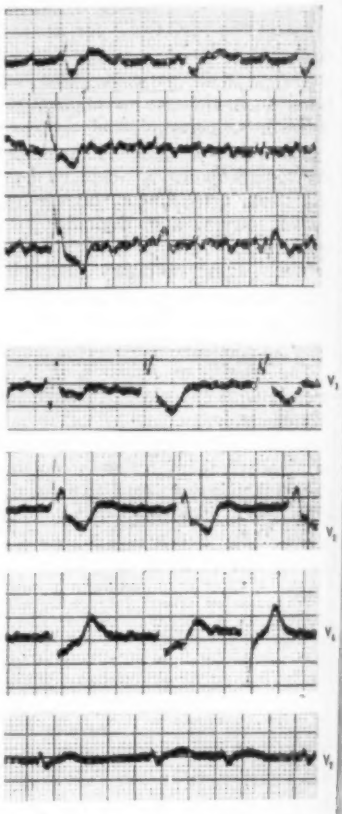

FIG. 4.—Case 6. E.C.G. 3 days after admission.

Case 4 appears to demonstrate transaminase levels confirmatory of recent infarction before fully diagnostic electrocardiographic changes had occurred. In Case 5 the transaminase level again agreed with the proved diagnosis in the absence of confirmatory E.C.G. changes. The raised serum bilirubin level might be expected to cause a rise in transaminase values due to the high transaminase content of bile. However, the results in this case were consistent with the proved diagnosis at necropsy.

Case 6 was also proved at necropsy despite non-confirmatory electrocardiography and in the presence of carcinomatosis.

Case 7 reveals apparently diagnostically raised transaminase values, whereas the electrocardiographic changes are merely suggestive. Although permission for necropsy was not obtained there is felt to be no doubt on purely clinical grounds about the diagnosis.

Cases 4 to 7, therefore, are instances in which transaminase levels proved of greater diagnostic aid than initial electrocardiography.

(15) *Case 8.*—Man aged 76. Diabetic; sudden collapse and death in two hours; no prior history of cardiac pain. Serum transaminase: 36 SGO-T units at onset of collapse. E.C.G.: postero-lateral infarct three days *before* collapse. Necropsy: fibrotic myocardium; 2-cm. thrombus in right coronary artery proximal part several (? 10) days old, distal part quite fresh.

(28) *Case 9.*—Woman, aged 76. Hypertensive "collapse" 10 days previously. Serum transaminase: 20 SGO-T units 10 days after collapse. E.C.G.: antero-lateral infarct six days after collapse; much improved 13 days after collapse. Recovered.

Cases 8 and 9 illustrate the need for transaminase levels to be estimated at the appropriate times after infarction if they are to prove of help in assessment. Thus in Case 8 the estimation was too soon after the terminal infarction to reveal any change, and in Case 9 the time interval of 10 days after infarction is too long. The optimum times after infarction appear to be from 24 hours to five days.

(7) *Case 10.*—Woman, aged 55. Depressive; hypertension; five hours' epigastric pain. Serum transaminase: 83 SGO-T units 48 hours after onset, 47 units at 3 days, 16 units at 4 days. E.C.G.s taken 48 hours and 10 days after onset are shown in Figs. 5 and 6.

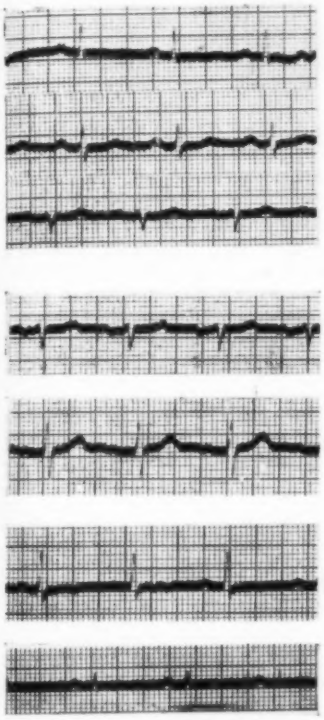

FIG. 5.—Case 10. E.C.G. 2 days after onset.

If serum transaminase levels prove a reliable guide the test will be of extreme value in this type of case, where the infarct is presumably small, in that a more definite prognosis may be given. A negative result (normal transaminase levels) would be of equal value. This was the only case of this type in the present series.

Of the 31 cases of myocardial infarction, 23 occurred clinically within seven days prior to serum transaminase estimation being obtained. Of the 23 patients with acute infarctions, 16 recovered and 7 died (see Table). The 16 recoveries reveal an average peak transaminase value of 111 SGO-T units. The deaths reveal an equivalent average figure of 576 SGO-T units. These figures are not altogether accurate, as in a few of the recovered cases the transaminase levels obtained were not necessarily the highest that actually occurred. Similarly in the fatal group, one case reveals a low value as it was too soon after infarction to expect a rise, and one patient with infarction died from bronchopneumonia and carcinomatosis rather than the infarct, and consequently the low value obtained agrees with the necropsy findings of a small infarct.

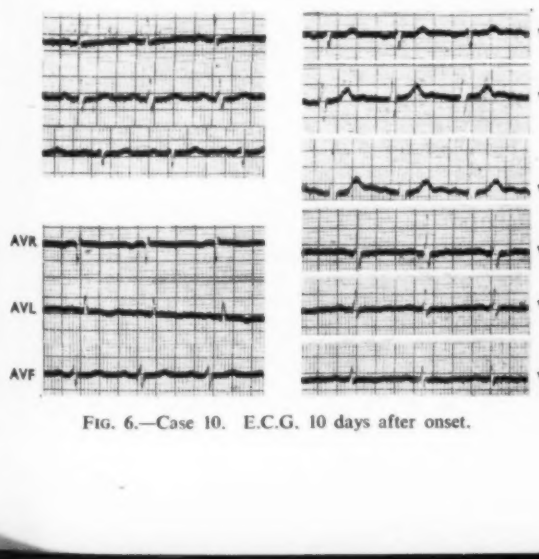

FIG. 6.—Case 10. E.C.G. 10 days after onset.

Results in 23 Cases with Acute Infarctions

Case No.	Observed Serum Transaminase Peak Values	Outcome	Necropsy
2	216 units 56 hours after onset	Recovered	
3	184 ,, 12 ,, admission	,,	
4	160 ,, 24 ,, onset	,,	
5	460 ,, 1 day after admission	Died	Extensive infarct of both ventricles
6	86 ,, 6 days ,, ,,	,,	Recent circumflex artery occlusion
7	550 ,, 5 days after onset	,,	No necropsy
8	36 ,, at the time of infarct	,,	Old and recent infarcts
10	83 ,, 48 hours after onset	Recovered	
12	200 ,, 36 ,, ,,	,,	
13	61 ,, 78 ,, ,,	,,	
14	120 ,, 12 ,,	,,	
15	73 ,, 5 days after admission	,,	
16	43 ,, 24 hours after onset	,,	
17	129 ,, 12 ,, ,,	,,	
18	41 ,, 7 days ,,	,,	
19	95 ,, 3 ,, ,,	,,	
20	900 ,, 3 ,, ,,	Died	No necropsy
21	156 ,, 32 hours ,,	Recovered	
22	24 ,, 4 days ,,	,,	
23	280 ,, 48 hours ,,	Died	Extensive infarct
24	114 ,, 33 ,, ,,	Recovered	
25	75 ,, 48 ,, ,,	,,	
26	1,720 ,, 48 ,, admission	Died	No necropsy

These points would possibly cause a higher average figure in the recoveries, but also would increase the figure in fatal cases, and it is felt, therefore, that the difference is probably significant.

The average time of peak transaminase level relative to the time of infarction was estimated from cases where serial transaminase levels were known. Where the time of infarction was in doubt it has been accepted as from the moment of admission. The average figure so obtained was 62 hours after infarction in the 18 suitable cases.

Serum transaminase estimations were carried out both during and for several days after attacks of angina in appropriate cases. On each occasion the transaminase value was found to be within the normal range. On several occasions, in two cases of old myocardial infarction with recurrent attacks of angina, we found transaminase value of help in distinguishing prolonged anginal pain from that due to further myocardial infarction, the transaminase values correlating well with subsequent electrocardiography and clinical progress.

In this series the overall average age of the patients with myocardial infarction was 60 years. The average age of the males was 58 years, and of the females 67.

Discussion

It is appreciated that the majority of cases of myocardial infarction can be diagnosed on clinical grounds, but a group remains in which the diagnosis is initially in doubt.

This small series of cases confirms reports in America and this country that recent myocardial infarction can be detected in some cases by a typical rise and fall in serum transaminase values before diagnostic electrocardiographic changes have occurred. The correlation of degree of rise in serum transaminase level with size of infarct and immediate outcome suggests that transaminase values of over 250 units are of serious portent and such cases are unlikely to recover.

The importance of time of transaminase estimation after infarction was well shown in several cases. It is suggested that transaminase values should be estimated at 24-hourly intervals from the time of infarction for at least four and preferably seven days, or until the peak value is passed, if full information is to be obtained from the results.

In differential diagnosis, too, the transaminase levels may be of help. On several occasions we found it useful in assessing whether severe cardiac pain was due to prolonged angina pectoris or actual infarction, the transaminase results correlating in each case correctly with electrocardiographic findings and subsequent clinical progress.

No diagnostic rise in transaminase levels was detected in two cases of pulmonary infarction, two cases of gall-bladder dysfunction, two cerebral catastrophes, and six cases of pneumonia.

It is of interest that one case of active rheumatic pericarditis (not included in this series) revealed a transiently raised serum transaminase level. This suggests concurrent myocardial damage of a temporary nature, and it will be of interest in the future to ascertain whether serum transaminase levels will help in assessing activity in cases of rheumatic carditis where this is in doubt.

In carrying out these estimations of serum transaminase levels the method of Frankel and Reitman (1957) was found to have several inherent disadvantages regarding cost and technique. These seem to be overcome in the method described by King (1958), and the simpler technique and its cheapness should place it well within the scope of all routine laboratories.

Summary

Serum transaminase estimations in a small number of cases of myocardial infarction are related to clinical, electrocardiographic, and necropsy findings. The test's possible value and advantages in early differential diagnosis and prognosis are discussed.

This series reveals close correlation between peak transaminase levels, size of infarct, and immediate outcome.

Evidence is presented which shows that cases in which transaminase values rise above 250 SGO-T units do not usually recover.

We thank Dr. R. Mowbray and Dr. T. A. Grimson for permission to publish this report and for their interest and encouragement, Dr. J. Ennis for his help in assessing the pathological findings, and Miss Haigh for her unstinted secretarial help.

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Rank Precision Industries (B.A.F.) Ltd. has issued a leaflet describing the films and filmstrips on hospital and medical training in the G.B. Film Library. The leaflet lists 44 films and 33 filmstrips which are available from the library. It gives brief details of their length, number of reels or frames, hire rates, and purchase prices. Handbooks containing essential information for the guidance of teachers or film users are supplied with the films and filmstrips. Films are available for either outright purchase or hire; viewing copies will be supplied free of charge on application. Filmstrips are for outright purchase only, but may be previewed under a 14-days "sale or return" approval scheme. Further details from the G.B. Film Library, Aintree Road, Perivale, Greenford, Middlesex.

SCURVY FOLLOWING BILATERAL ADRENALECTOMY

REPORT OF TWO CASES

BY

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During the convalescent period of two patients who had undergone bilateral adrenalectomy and oophorectomy for advanced breast cancer it was noticed that they developed petechial skin haemorrhages on the arms and legs. One of these patients also complained of bleeding gums. A diagnosis of scurvy was made and the vitamin-C saturation test was carried out. In the first patient only 21 mg. of the vitamin appeared in the urine, following an intravenous injection of 1,000 mg. of ascorbic acid, and in the second case only 31 mg. was excreted. The average amount of ascorbic acid excreted during this test in a normal healthy individual varies between 300 and 500 mg.

These findings stimulated us to investigate two other patients in the ward who had recently had their adrenals and ovaries removed, and in both cases the test showed a vitamin-C deficiency. Further patients were investigated and of nine who were subjected to the test similar deficiencies were found in seven. The remaining two patients had been operated upon several months previously; both had progressed well, had good appetites, and had increased in weight, and in them the values were 370 and 570 mg. respectively. The average amount of vitamin C excreted in the seven patients (average age 53 years) in whom the figure was low was 85 mg.

A control series of tests was carried out on nine patients who had recently undergone operations such as radical mastectomy, cholecystectomy, appendicectomy, and colectomy. The average amount of vitamin C excreted by them was 300 mg., their average age being 49 years. None of these patients had been given vitamin C therapeutically.

Although there is some doubt about the reliability of the vitamin-C saturation test, these figures seemed significant and led us to believe that patients who had both adrenals and ovaries removed might be deficient in vitamin C, especially in the early post-operative period.

We record the two case histories of scurvy following bilateral adrenalectomy and oophorectomy, and discuss the possible cause of this, together with the relationship of vitamin C to the adrenal glands.

Case 1

A housewife aged 37 was admitted to hospital on June 17, 1958. Nine months earlier she had noticed a swelling in the left breast which had ulcerated through the skin. She complained of loss of energy, tiredness, and poor appetite. On examination she had a foul-smelling, fungating cancer of the left breast, with an infected carcinomatous ulcer in the left axilla. She was pale and listless, with oedema of the legs and sacrum. A blood count showed a haemoglobin level of 22%, and 16,600 white blood cells, of which 95%

were polymorphonuclears. *X*-ray examination of the chest revealed secondary carcinomatous deposits in the mediastinum and ribs.

Following a blood transfusion a right adrenalectomy and bilateral oophorectomy was carried out on June 19. The left adrenal gland was removed two weeks later. Her general condition improved after the second operation, but some days later she developed a temperature, and pus from an infected haematoma began to discharge from the wound in the right loin. Culture of the pus from the breast and

FIG. 1.—Case 1. Petechial haemorrhages of scurvy on the hands following bilateral adrenalectomy.

the loin showed a heavy growth of *Staphylococcus aureus*, sensitive to chlortetracycline and erythromycin.

On the eleventh post-operative day she developed purpuric spots on the hands (Fig. 1), arms, and abdomen, together with sore bleeding gums. At this time she was taking a normal well-balanced diet. A blood count showed a haemoglobin level of 72%, white cells 18,600 with 95% polymorphs, platelets 210,000, and a bleeding-time of 6½ minutes. A diagnosis of scurvy was made, and the vitamin C saturation test revealed a marked vitamin-C deficiency, there being only 21 mg. of ascorbic acid excreted in the urine.

She was given 300 mg. of ascorbic acid daily by mouth, and the rash eventually disappeared. Following a course of deep *x*-ray therapy to the ulcerating breast, which had become a little smaller and cleaner, she was sent home on August 8.

Case 2

A housewife aged 62 was admitted to hospital on June 28, 1958, having had a radical mastectomy in January, 1957, for an anaplastic round-celled carcinoma of the left breast. She had developed secondary carcinomatous deposits in the skin

FIG. 2.—Case 2. Subcutaneous haemorrhages of scurvy on the thigh following bilateral adrenalectomy.

of the right chest wall, and an *x*-ray examination showed lung deposits and a pleural effusion. Her haemoglobin level on admission was 82%.

On June 30 a left adrenalectomy and bilateral oophorectomy was carried out. The liver was found to contain extensive deposits of secondary growth. The adrenal gland was infiltrated with carcinoma, and this was confirmed on histological examination. Ten days later a right adrenalectomy was performed, but a week later her right loin wound became infected following the discharge of a haematoma. She also developed multiple bedsores, which became infected. At this stage she was being given a high-protein diet, but was reluctant to eat.

Culture of the pus in the wound revealed a growth of *Staph. aureus*, which was insensitive to all antibiotics except novobiocin, which was given in doses of 250 mg. six-hourly for five days.

On the tenth post-operative day she developed purpuric spots and haemorrhages on the hands, arms, and legs (Fig. 2). The gums appeared normal, but she was edentulous. A blood count showed a haemoglobin level of 71%, white cells 13,300 with 94% polymorphs, platelets 47,000, and a bleeding-time of 3½ minutes. A vitamin-C saturation test was carried out and 31 mg. of ascorbic acid was excreted.

She was given 300 mg. of vitamin C daily and the purpuric spots diminished in number, but did not disappear as in Case 1. Although her wounds became cleaner and began to heal, her general condition deteriorated and she died on August 1.

Discussion

It is possible for most vitamins, an exception being vitamin C, to be synthesized in the body, and we depend entirely on extraneous sources for our essential requirements of it. It can be stored to a limited extent in the body, and this is said to occur mainly in the adrenal cortex, pituitary body, corpus luteum, and lens. Investigations have shown that the guinea-pig behaves in a similar way to man and cannot synthesize the vitamin, whereas the rat, dog, and mouse are able to do so. The site of this synthesis is not known, but it may be in the adrenals, as Dumm and Ralli (1949) observed that the ascorbic acid excretion by rats after bilateral adrenalectomy fell to low values. On the other hand, the synthesis is not entirely dependent on the adrenals, as adrenalectomized dogs and rats can be maintained on a vitamin-C-free diet.

A great deal of experimental work has been carried out to determine the relationship between ascorbic acid and the adrenal cortical hormones. In animals, following stress or the administration of corticotrophic hormones, the increased secretion of adrenocortical hormones is associated with a rapid decrease in the amount of ascorbic acid and cholesterol in the adrenal gland. There appears to be considerable doubt about the relation of vitamin C to the synthesis of the adrenocortical steroids. In persons dying after continuous stress the enlarged adrenals were found to contain about 50% less than the normal amount of ascorbic acid and cholesterol (Uotila and Pekkarinen, 1951).

That ascorbic acid is not essential for the actual synthesis of the hormones is seen in scorbutic animals, when cortical hormones are elaborated in the absence of the vitamin. On the other hand, when the adrenals are removed from guinea-pigs, and vitamin C is withheld, the animals die rapidly (Clayton and Prunty, 1953). In classical cases of scurvy in man, the typical findings of eosinopenia and increased 17-ketosteroid excretion are noted after corticotrophin therapy and are not changed after vitamin C administration. After saturation with vitamin C there is a marked increase in urinary ascorbic acid following treatment with corticotrophin.

The effect of corticoid release on ascorbic acid excretion in man is described by Stefanini and Rosenthal (1950) and by Holley and McLester (1951). In each case two male patients with rheumatoid arthritis were treated with cortico-

trophin for periods of six months. In all four patients symptoms of scurvy developed which responded to vitamin C. Holley and McLester have suggested that ascorbic acid plays the part of a reducing mechanism in the production of the steroid hormones. In order to conserve the ascorbic acid content of the adrenal cortex, the body is apparently able to deplete other structures. Corticotrophin therapy reduces the stores of ascorbic acid in the adrenal cortex, and prolonged administration produces a deficiency and symptoms of scurvy.

Kayahan (1952) states that following the taking of large doses of vitamin C by mouth in man, there is an increased corticoid but decreased 17-ketosteroid excretion in the urine, indicating a direct action on the adrenal cortex.

Finally it has been shown that ascorbic acid is used up more rapidly when infection is present.

Summary and Conclusion

The adrenal cortex is the main storage depot of vitamin C in man.

The release of cortical hormones is associated with an increased excretion of ascorbic acid and a reduction of the ascorbic acid content in the gland itself.

Large oral doses of vitamin C appear to increase corticoid but decrease 17-ketosteroid excretion in the urine, indicating a direct action on the adrenal cortex.

It is open to discussion whether or not vitamin C is concerned with the actual synthesis of the adrenocortical steroids, but it is suggested that the power of the adrenal cortex to secrete the hormones is dependent on the presence of ascorbic acid.

In the cases of scurvy described here it is significant that infection was present in each case, and also in another patient with a low ascorbic acid excretion. Infection was not recorded in any other case which had undergone bilateral adrenalectomy. The presence of infection is believed to cause vitamin C to be utilized more rapidly, and thus deplete the limited reserves. We believe that patients who have their adrenal glands and ovaries removed tend to have a lowered reserve of the vitamin immediately after the operation. This belief is based on the finding of a low vitamin excretion in seven patients following adrenalectomy and oophorectomy, and comparing these values with a group of patients who were recovering from other types of operation.

We suggest that these cases should receive an adequate intake of ascorbic acid if they are not to develop deficiency symptoms.

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The National Council of the National Deaf Children's Society held its first meeting on October 18. The constituent societies are the former Deaf Children's Society, which has amended its constitution to become a national organization, and the following affiliated regional associations: the Herefordshire and Worcestershire Association for Parents of the Deaf; the East of Scotland, the Hertfordshire, the Oxford and Districts Regions; the N.-E. and N.-W. Deaf Children's Associations; and the South Wales Parents' Association for Deaf Children. The Society's address is: 1, Macklin Street, Drury Lane, London, W.C.2.

SURGERY OF ATRIAL SEPTAL DEFECTS

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The shunting of significant amounts of blood from the left to the right atrium through a septal defect should in most cases be corrected surgically. Whether this is performed by the closed method, as devised by Gross *et al.*, or by suture under the direct vision with hypothermia, as first practised by Lewis *et al.* (1955), will depend upon the practice of the individual clinic. In this unit open heart surgery is the method of choice, combined with hypothermia.

Surgical Anatomy

This has been dealt with in many communications (Rokitansky, 1875; Hudson, 1955; Lewis *et al.*, 1955; Ross, 1956; Bedford *et al.*, 1957).

Three main types of defect may be found, and any of these may be associated with anomalous pulmonary venous drainage: (1) The high defect, or sinus venosus type, is always associated with some anomaly of pulmonary venous drainage. There is no postero-superior margin, and the upper portion lies within the mouth of the superior vena cava (Fig. 1). (2) The fossa ovalis or ostium secundum defect. These are well-defined anteriorly, and there are a number of variations as seen in Fig. 2, A, B, and C. (3) The ostium primum defects. The anterior margin of the defect in these cases is formed by the ventricular septum. These ostium primum defects are associated with other anomalies, particularly a cleft mitral valve, producing mitral regurgitation, but the tricuspid valve and the upper portion of the ventricular septum may be deficient (Fig. 3).

Clinical Findings and Catheter Studies

Excellent clinical descriptions of the conditions are available (Kjellberg *et al.*, 1955; Wood, 1956; Bedford *et al.*, 1957; and many others). In the uncomplicated cases with a low pulmonary vascular resistance the findings are those that would be expected when many litres of blood escape from the left to the right atrium and pass through the right heart and pulmonary bed. The right ventricle is overactive and the increased blood flow gives rise to a pulmonary systolic murmur audible along the left sternal edge. There may be a thrill associated with the murmur. Characteristically, the second sound is widely split and fixed. In most cases a tricuspid diastolic flow murmur is audible on inspiration. This, like the pulmonary systolic murmur, is due to the torrent of blood flowing through the right heart. The radiograph shows the characteristic findings of an enlarged right atrium and pulmonary artery with varying degrees of pulmonary plethora and in association with a small aorta. In the secundum type the electrocardiogram shows right ventricular hypertrophy and a partial right bundle-branch block type of pattern.

All cases have been subjected to cardiac catheterization with the object of confirming the clinical diagnosis and of determining the pulmonary resistance and the magnitude of the shunt. This has sometimes been useful in determining whether anomalous pulmonary venous drainage is present. A gradient across the pulmonary valve does not necessarily mean that there is associated pulmonary valve stenosis, because a significant gradient can be produced by a large flow across a normal valve. In one case there was a considerable gradient across the valve, the right ventricle pres-

sure being 60/0 and the pulmonary artery pressure 18/6. After closure of the defect the thrill in the pulmonary artery disappeared and the right ventricular pressure dropped to 28/4 with a pulmonary artery pressure of 20/10.

Indications for Surgery

The volume of the shunt has been the indication for surgery, not the presence or absence of symptoms in the patient. Ideally, the shunt should be arrested before the right heart has developed permanent secondary organic changes.

The closure of a proved atrial septal defect can now be regarded in the same light as a persistent ductus; that is, to prevent the ill effects of the shunt on the heart and pulmonary bed. It is quite wrong to wait for the development of symptoms.

In the pre-operative assessment, the presence and volume of the shunt and the level of the pulmonary vascular resistance are all taken into consideration. Shunts of 2 : 1 or more are considered suitable for surgery, while a raised pulmonary vascular resistance (particularly with a small shunt) makes surgical closure hazardous. The late development of cyanosis as a result of reversal of the shunt is an absolute contra-indication to surgery.

The electrocardiogram must show right ventricular hypertrophy and right axis deviation. Right axis deviation is of some importance, since a tendency to a left axis deviation may suggest an ostium primum defect. In the two ostium primum defects we have encountered, left axis deviation has been present and we do not now operate in such cases.

Cases in failure and those in the older age group should not be excluded provided that the pulmonary vascular resistance is not raised and the agreed indications are present, but a higher operative risk may have to be accepted. On the other hand, this must be set against the unfavourable natural history of the disease. The average age at death in three published series is as follows: Roesler (1934), 36 years; Welch and Kinney (1940), 33 years; and Burrett and White (1945), 39 years.

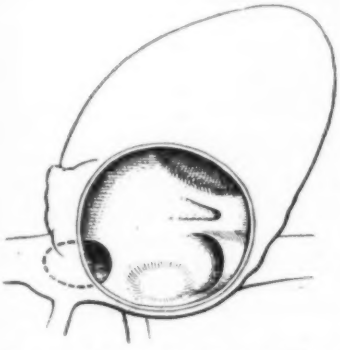

FIG. 1.—Sinus venosus, or high defect. These cases are associated with one or more anomalous veins draining into the dilated superior vena cava.

Clinical Analysis

This surgical series consists of 49 cases—46 secundum defects, 2 primum defects, and 1 sinus venosus defect. The Table shows the age distribution in relation to symptoms. It will be seen that 18 cases in this series had symptoms.

Age Distribution

Age:	0–5	6–10	11–15	16–20	21–30	31–40	41–50	51–60
No. ..	1	2	8	4	5	0	8	1
Symptoms	0	1	3	1	4	0	8	1

The sex distribution consists of 12 males and 37 females. The majority of those with symptoms complained of dyspnoea on moderate exertion accompanied by palpitations. Recurrent chest infection was present in four and two had suffered haemotypsis. Frank cardiac failure had been present in five and their ages were 30, 47, 48, 49, and 56. The patient over 56 had been virtually incapacitated for 18 years. This group survived surgery and has done well, except for the patient of 56, who succumbed during surgery. This was due to a heavily calcified pericardium around the inferior vena cava, which made the dissection of this vessel hazardous. After release of the clamp across the inferior vena cava it was found that the calcium had produced disruption of the vessel wall, with uncontrollable haemorrhage. The patients with symptoms were, in the main, over the age of 20, but those with recurrent chest infection were in the younger age group and had been investigated elsewhere for bronchiectasis. There was one further case in failure; this was in a child with an ostium primum defect.

It has been stated that there is retardation of growth in these cases; certainly in our series there were several patients who were quite definitely undersized.

Anaesthesia is to be fully described elsewhere by Dr. E. S. Machell.

Surgical Technique

This type of surgery must be carried out by a team fully trained in this work, and the operating team must be thoroughly integrated with the anaesthetic and nursing teams. All the steps in the

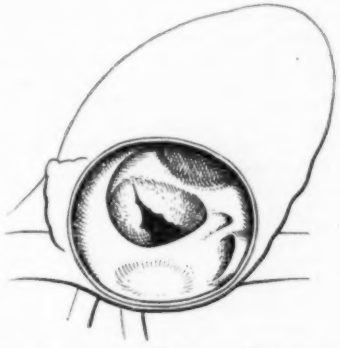

FIG. 3.—An ostium primum defect. It is well defined posteriorly, but the anterior margin is formed by the ventricular septum. The mitral valve is deeply cleft.

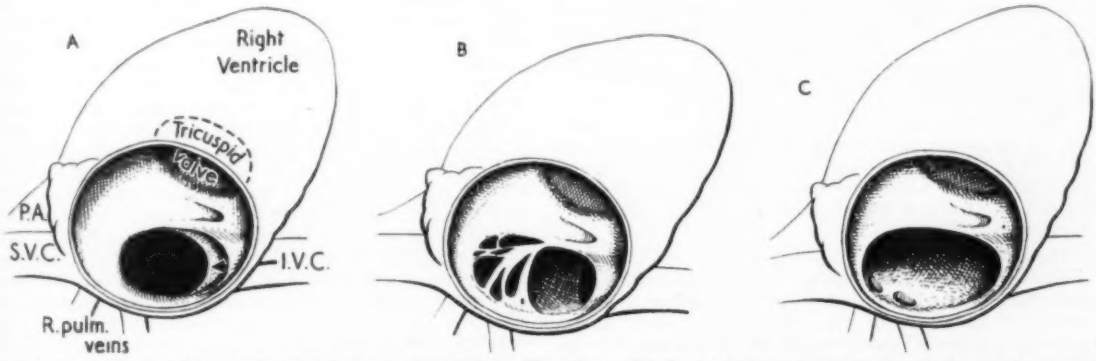

FIG. 2.—A, Typical fossa ovalis or ostium secundum defect. There is a well-defined anterior margin. B, Lacework type of ostium secundum defect due to incomplete remnants of the septum primum. C, Large ostium secundum defect. Note how the inferior margin is overlapped by the eustachian valve. There are two apparently anomalous pulmonary veins visible.

operation must be carefully rehearsed, and each member must know precisely what function he is to serve.

The approach is through the bed of the fourth rib on both sides, with transection of the sternum. The mediastinum is inspected for a left-sided superior vena cava. Rubber slings are placed around the superior and inferior vena cava, so as to occlude these vessels. The defect is then explored digitally through a small incision made in the wall of the right atrium. This exploration should be done systematically to exclude anomalous pulmonary veins and to note the relationship of the eustachian valve to the inferior vena caval opening. The defect is then explored to confirm the diagnosis of ostium secundum defect. The observer, having obtained a clear conception of the interior of the atrium, then withdraws his finger and the atrium is explored digitally by an assistant.

The anaesthetist acts as the timekeeper and times the occlusion of the superior and inferior venae cavae. After 20 seconds the aorta is cross-clamped and neostigmine is injected proximal to the clamp in order to perfuse the coronary circulation. A transverse sinus clamp is then applied across the pulmonary artery and the aorta as low down as possible and the right atrium is opened widely. Any blood remaining is sucked out and a careful survey of the anatomy made. A stitch is then placed through the lower end of the defect and another is placed in the upper end, after which the intervening defect is closed with a running suture. There are often lacework remnants of septum primum across the defect, and these are incorporated in the suture. The needle must pick up the limbus of the fossa ovalis. A further one or two additional interrupted sutures are placed. Before closure of the defect, to exclude air from the left atrium, the anaesthetist inflates the lungs in order to force blood from the left atrium and to expel any trapped air. To exclude air from the right atrium the inferior vena caval snare is released to fill this chamber with blood. A clamp is then placed across the atrial incision, while the transverse sinus clamp is slowly released. The superior vena cava can then be released. At this stage the operator proceeds with closure of the atrial wall, while another member of the team watches the heart for arrhythmias and the coronary arteries for air embolus. If ventricular fibrillation occurs, the member at the table opposite the surgeon massages the heart while the atrial closure is completed.

Most of the cases have had a period of atrial fibrillation during hypothermia. Every case except one has reverted to sinus rhythm before leaving the theatre. One remained in atrial fibrillation but was restored to sinus rhythm two weeks later with quinidine.

Bilateral drainage tubes are inserted up to the base of both pleural cavities and connected to underwater drainage.

Post-operative complications have been few, and are to be discussed by Dr. Machell elsewhere.

Deaths

In this series of 49 cases there have been four deaths. The deaths occurred in the first 10 cases and there have been none in those following. Hypothermia alone has not been primarily responsible for any deaths, and we consider it to be a safe procedure.

The first death was in a woman of 44 and was an early case in the series. She should not have been operated on, and this was a case of bad selection. She had severe symptoms and a high pulmonary resistance with a small shunt. In the light of present knowledge she would not be accepted for surgery.

The second death was due to a technical error. This was during the closure of a low defect in association with a large eustachian valve, and, while the dangers of this combination were well known to us, this case occurred early in our experience, and was further complicated by associated anomalous venous drainage. The edge of the eustachian valve was mistaken for the lower edge of the defect and incorporated in the suture. This deviates the inferior vena caval blood into the left atrium. The mistake was not appreciated at the time, and the patient succumbed.

The third case was that of a woman of 56 whose death from haemorrhage has been recorded above. The fourth was that of a child of 12, in whom an attempt was made to close an ostium primum defect. She developed complete heart-block and succumbed in 36 hours. While it is technically possible to close primum defects under hypothermia, the limited time available does not allow adequate margins of safety; but Kirklin *et al.* (1955) have shown that these defects can be closed successfully by inserting a prothesis, using the heart–lung machine.

Follow-up

At the follow-up all survivors were symptomatically well and all the defects have been assessed by our cardiologist, Dr. R. V. Gibson, as being closed, except in one case in which he thinks there may still be a small shunt. This shunt must certainly be small, as the child has improved and has grown remarkably in six months. This child is to be recatheterized. We have not routinely recatheterized our post-operative cases unless there was the slightest doubt clinically that the defect was completely closed. The three cases catheterized post-operatively have shown no residual shunt.

Summary

A series of 49 cases of atrial septal defects have been closed under hypothermia by surface cooling. Two of the defects were of the ostium primum variety, one a sinus venosus defect, the remaining 46 being ostium secundum defects. There were four deaths among the first 10 cases and none in the last 39 cases.

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The W.H.O. Expert Committee on Malaria at its meeting in Lisbon in September last reviewed the role of antimalarial drugs in world-wide malaria eradication, especially in the later stages of the campaign. If malaria eradication among stable populations in towns or villages was comparatively easy, it became very difficult among nomads—for instance, Bedouin or Amazon-Indian tribes and migrant workers, or groups of people usually dispersed, such as labourers, woodcutters, or fishermen, who lived in tents or temporary shelters. One possible way to protect these groups from malaria appeared to be medicated salt (Pinotti's method). Common household salt was mixed with antimalarial drugs and became a part of the normal diet of people exposed to malaria. This method had been tried out for several years in Brazil, and soon would be applied to more than a million people in that country. Experimental trials had been carried out in the United States under W.H.O. sponsorship, and the application of this method in the field was planned in several other countries. In some parts of Africa experiments were well under way in order to assess possibilities of using Pinotti's method, while more general experiments connected with the distribution of drugs were being attempted almost everywhere in that continent.

PUBLIC HEALTH ASPECT OF TUBERCULOSIS IN DOMESTIC ANIMALS*

BY

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The first advice to take interest in animal diseases came from Hippocrates, the Father of Medicine, who frequently refers to the usefulness of comparative pathology in its application to human medicine. He tells us that his observations on the hydatid cysts in the brain of goats helped him to use this information to combat the prevalent idea that human epilepsy was produced by demons. I shall not be able to change your views to such an extent; I hope only to contribute to a better understanding of the comparative pathology in tuberculosis.

It is difficult to deal with the comparative pathology of tuberculosis and with the possibility of mutual infection of animals and man without saying something about the history of tuberculosis in animals. Although tuberculosis in man is a disease of great antiquity and tuberculous lesions were found in the bones of Egyptian mummies, there is no clear evidence suggesting that tuberculosis existed in animals at the same time. Some old manuscripts mention the diseases of lungs in cattle, but we do not know whether they refer to pleuropneumonia or to tuberculosis. Keppler (1649) and Florini (1702) were the first to describe tuberculosis in cattle on a scientific basis. Of the various forms of tuberculosis in animals so-called pearl disease in cattle long ago attracted general attention, and the regulations concerning meat inspection in various countries included it. The disease was generally accepted as a syphilis and was called "French disease."

The proper study of tuberculosis in cattle started in the eighteenth century, when town dairies began to supply the manufacturing towns with milk and the incidence of tuberculosis was high.

Effect of the Industrial Revolution

There is no doubt that the industrial revolution played a great part in increasing the prevalence of tuberculosis, not only in man but also in animals. This disease is almost unknown among native cattle in prairie regions of South America or in the Steppes of Russia, or among sheep in any country, but it increases in prevalence as the larger towns are approached and intimacy of contact with overcrowded towns becomes closer. During the first half of the last century some authors regarded pulmonary tuberculosis in man and in animals as identical, while others, particularly Virchov, disputed the occurrence of tuberculosis in animals altogether. According to his view the lesions in the lungs and serous membranes were sarcomata which might be considered identical with lymphosarcomata of man.

Later experiments have shown not only that tuberculosis is infectious but also that it is transmissible by means of injection or through inhalation. This was proved in 1868, but it was not until 1910 that the exact relationship of the human, bovine, and avian types of infection and the transmission from one species to another were fully understood.

Before dealing with the character of the disease in various animals I will make a few general remarks on transmission and its results. The evidence supporting the widely accepted view that the chief route of infection in both man and cattle is via the respiratory tract has been challenged by various workers. They maintain that infection mainly starts in the intestinal tract and that the significance of the lung and regional lymph node lesions as an indication of the route of infection is not very convincing, since the tubercle bacillus could pass through the intestinal wall and localize in the pulmonary tissues without leaving any trace of its paths through the abdominal cavity. Edwards (1937) studied the role of alimentary infection in the calf naturally infected with the bovine type of *Mycobacterium tuberculosis* for a period of 12 weeks. Out of 36 calves, 34 reacted to tuberculin, and at necropsy a careful naked-eye examination of the mesenteric glands failed to show the presence of visible lesions, whereas tubercle foci were found in the thoracic glands and in the lungs of every calf that was affected.

Soltys and Jenning's (1950) experiments on dissemination of tubercle bacilli in guinea-pigs showed that tubercle bacilli inoculated subcutaneously were present in various organs and in the urine and faeces after a few hours, depending on the number of bacteria inoculated. No gross or microscopical lesions were noted in kidneys or mesenteric lymphatic nodes in the first five days, although tubercle bacilli were present in these organs. These experiments support the view of workers that the lung and regional lymph node lesions are not indicative of the route of infection, but are only an indication of the different affinity of various tissues to different types of tubercle bacilli.

Cattle

In the great majority of cases bovine tuberculosis occurs as a localized disease in which the lesions are of chronic and slowly progressive type with much connective tissue hyperplasia, caseation, and a great tendency to calcification. Bovine tuberculosis is always caused by virulent tubercle bacilli of bovine type. Human and avian tubercle bacilli in bovines have rarely been found in naturally acquired tuberculosis. In respect to tuberculous lesions it appears that of all animals the cow is the one most comparable to the human being. Of all tuberculous lesions in cattle, infection of the udder is of the greatest importance from the public health point of view as bacilli are excreted in milk. Bovine tubercle bacilli may often escape in milk of tuberculous cows even when there are no detectable lesions in the udder.

Tuberculosis in the mammary gland of the human being is a very rare finding, in contrast to its high frequency in the cow. The constant and high degree of activity in the animal may be an influential factor.

It is gratifying that the situation concerning control of tuberculosis in cattle is improving very rapidly in this country. Of the total cattle population (10,047,000), 73% are tuberculin-negative, and registered as attested herds (see Table). The remaining 27% do not belong to attested herds, and there is no doubt that a certain number of animals among them are tuberculous.

Area Eradication Plan for Tuberculosis Attested Herds Scheme, 1950. Statement Showing the Position in Great Britain as at October 1, 1957

	Total Cattle on June 4, 1957. (Provisional Figures)	No. of Registered Attested Herds	Total Attested Cattle	Percentage of Total Cattle
England	7,176,000	102,969	4,751,000	66
Wales	1,076,000	36,213	985,000	92
Scotland	1,795,000	41,689	1,617,000	90
Total ..	10,047,000	180,871	7,353,000	73

Tuberculosis in Sheep and Goats

Sheep are apparently just as susceptible to the bovine type of *Myco. tuberculosis* as cattle, but it is rare indeed to find a case of bovine tuberculosis in sheep, whether in

*Address to the British Tuberculosis Association given on March 28, 1958, in Cambridge.

Britain or abroad, and it is difficult to escape the belief that the different picture is consequent upon their way of life, as they are never housed. Most of the cases of tuberculosis in sheep are due to the avian type (Griffith, 1925; Creech, 1940). While it is impossible to trace the source of infection, it seems logical to conclude that wild birds, which are frequently infected with avian tubercle bacilli, are responsible for avian tuberculosis in sheep.

The rarity of the disease in sheep is confirmed by the statistics of the Bureau of Animal Industry in the United States. Out of 17 million animals slaughtered, only two were condemned because of tuberculosis. Information concerning tuberculosis in goats is very scanty, and with one or two exceptions tubercle bacilli obtained from tuberculous goats have been of the bovine type. Experimentally, goats and sheep can be readily infected with bovine tubercle bacilli. In naturally occurring tuberculosis in sheep and goats lesions were observed in the liver, lung, spleen, and lymph nodes, and on the pleura and peritoneum.

Tuberculosis in Pigs

The incidence of tuberculosis in pigs is an indicator of the amount of tuberculosis in cattle, people, and poultry in a given community, because pigs are susceptible to human, bovine, and avian types of tubercle bacilli.

Tuberculosis of pigs due to the human type of infection is rather rare. Information concerning percentage of human types varies: Gerbert (1939), in his studies on typing tubercle bacilli isolated from 50 tuberculous pigs, demonstrated 33 cases caused by the bovine type, 5 by the avian type, 3 by the human type, and 9 by mixed infection of avian and bovine types.

When infection of pigs by the human type of tubercle bacilli is known the fact should be of interest to those concerned with the public health. If the dissemination of human tubercle bacilli is occurring in a community in sufficient numbers to produce tuberculous lesions in pigs, it is reasonable to believe that the source of such pathogens is a potential danger to human beings.

Natural infection of pigs with human tubercle bacilli, which often occurs in pigs kept on the farm attached to sanatoria, seldom results in more than localized tuberculous adenitis.

The bovine type of the tubercle bacillus is capable of producing in pigs more severe and more widely disseminated tuberculosis than either of the other two types of the organism. Early spread via the blood is an outstanding feature, with the result that miliary lesions are common in the lungs, liver, spleen, and kidneys, with involvement of the bones and joints. While the incidence of the bovine type of infection in pigs has steadily declined as tuberculosis is being eliminated from cattle, the incidence of the avian type is still high. Pigs may be infected either from tuberculous poultry or from wild birds. Tuberculosis in pigs caused by the avian type is predominantly a localized disease of the lymph nodes of the alimentary tract. However, the disease may become widely distributed, with involvement of the liver, spleen, lungs, and kidneys.

Hermansson (1939) demonstrated that water in which a meat inspector and workers dealing with tuberculous pigs had washed their hands produced tuberculosis in guinea-pigs in 11 samples out of 16; similar results were obtained with towels. These experiments clearly show that working with meat and organs of tuberculous animals entails a considerable risk both for those engaged in the slaughtering and for those examining the meat, and may explain the frequency of skin tuberculosis in meat inspectors and butchers. Tubercle bacilli are also often spread to clean carcasses by using the same knife as for examining slaughtered animals.

Tuberculosis in Horses

Almost all cases of tuberculosis in the horse are due to the bovine type, and about half of the strains are of reduced virulence. A few cases of tuberculosis due to the avian type are on record, and one case due to the human type has been described by Griffith (1928a). No accurate figures concerning the incidence of tuberculosis in horses in this country are available. This is mainly due to the fact that horses slaughtered in this country because of old age, general disability, or illness are not examined by the veterinary surgeon or even by the sanitary inspector. Nieberle (1931) stated that in German knackeries between 1904 and 1924 0.14% of the horses were tuberculous. Magnusson (1944) reported that, in Sweden, out of 461,436 slaughtered horses in the years between 1921 and 1942, 433 were tuberculous. Statistics of the incidence of tuberculosis in horses in various countries of Europe show that the disease has been very rare in these animals. The disease is often insidious in its onset and protracted in its course, and may be clinically inapparent for a long time.

The chronicity of equine tuberculosis, the proliferative nature of the lesions with the formation of large tumour-like masses, the non-caseating character, and the difficulty of recovering acid-fast organisms are the main characteristics of tuberculosis in a horse. Equine tuberculosis has something in common with Boeck's sarcoid or sarcoidosis, and may even support the view that Boeck's sarcoid and all related lesions are a form of non-caseating proliferative tuberculosis. It is interesting that the tuberculin test in this highly resistant animal is less reliable than in the case of many cattle or pigs. The organs mostly affected include lungs, liver, spleen, and nasal mucosa. Many other organs have been reported from time to time as being affected in individual cases.

Tuberculosis in the Dog

Tuberculosis in the dog is relatively rare. The available figures are highly selective and mainly based on necropsy material. The incidence of tuberculosis in dogs in Great Britain varies between 4 and 6% (Lovell and White, 1941; Jennings, 1949). The disease is most common between 1 and 5 years of age and relatively rare in old dogs. The animal is equally susceptible to human and bovine strains of tubercle bacilli, but it is much more resistant than man or cattle. From the fact that after the experimental intravenous inoculation of moderate doses (0.001 mg. per lb. (0.0022 mg. per kg.) of body weight) lungs will show lesions while other organs often remain uninvolved, it is evident that the lung in the dog, as in most other animals, offers a good soil for the development of tuberculosis. According to most workers the human type occurs in nearly 70%, and bovine in 30% of cases. It is generally agreed that the dog often acquires tuberculosis from a tuberculous person in the household or in restaurants, hotels, workshops, etc. The organs most often affected are lungs 72%, liver 67%, pleura 49%, kidneys 48%, and peritoneum 32% (Hjärre, 1939). Serous membranes in general appear to be more often involved in the dog than in the cat or any other animal.

Many workers found that in the dog the tuberculin test, whether intradermal or subcutaneous, is of little value in the diagnosis of tuberculosis because the animal develops only a low and irregular degree of allergy.

Tuberculosis in the Cat

Cats have a strong resistance to infection with tubercle bacilli of human and avian type, but are susceptible to the bovine type. Although there are a few records of the human type isolated from cats, it is not possible to say whether mistakes were made during typing. Griffith (1926) considers that cats are sensitive only to the bovine type.

Cobbett (1926) and Kuwabara (1938) found cats resistant to the human type of tubercle bacillus. These workers' results were confirmed by me. I was able to infect a cat with a dose of 0.001 mg. of the bovine type, but failed to infect cats with a dose of 10 mg. of the human type. The incidence of tuberculosis in cats varies between 3.6 and 13%. As in the dog, most of the figures are highly selective and mainly based on necropsy material.

Available evidence indicates that in most instances the infection in cats has its portal of entry by way of the digestive tract. Milk containing bovine tubercle bacilli and consumed by cats is the obvious source of most infections in these animals.

Tuberculin reaction in the form of thermoreaction appears to be more reliable than intradermal reaction.

Tuberculosis in Birds

With the exception of pets such as the parrot and the canary, in which the human tubercle bacillus is sometimes encountered, tuberculosis in birds is caused by the avian type of *Myco. tuberculosis*. Practically all species of domesticated birds and wild birds are susceptible to the avian tubercle bacillus. Tuberculous lesions occur most often in the liver, spleen, intestinal wall, and bone marrow. Other organs, including the central nervous system, may also be affected.

Human beings have a high resistance to the organism of avian tuberculosis, and therefore every alleged case of avian tuberculous infection in man must be established by convincing evidence. Even though true avian tubercle bacilli are obtained from materials of human origin, one should be cautious in assuming that the organism was actually responsible for the morbid progress in which it occurred.

Captive Wild Animals

Griffith (1928b) points out that tuberculosis in warm-blooded animals living in the wild state is unknown, but, on the other hand, it is common in animals kept in zoological gardens and menageries. It is an interesting finding of Griffith (1928b) and Lovell (1930) that the proportion of attenuated strains of tubercle bacilli isolated from these animals is much higher than from human or bovine cases.

The Public Health Aspect

The numerous publications presenting evidence incriminating the bacilli of bovine tuberculosis as a cause of tuberculous infections of human beings need no comment. Pasteurization of the public milk supply is now almost universal, except for some rural populations. It is interesting to know that 72 out of 570 milk samples examined biologically by the Veterinary Investigation Centre, Cambridge, during 1957, contained tubercle bacilli. This need cause no surprise, as Cambridgeshire, the Isle of Ely, and neighbouring counties have a very small percentage of attested cattle. In spite of the great advances in control of tuberculosis in cattle, there will be a constant potential hazard so long as only a few infected animals exist.

The gains made in controlling bovine tuberculosis can be maintained only by recognition of the fact that constant vigilance is necessary. It must be realized that not only a tuberculous animal but also a tuberculous person infected with the bovine type may transmit the infection. There are many records of persons who infected herds of cattle. Magnusson (1941) reported an instance where in a herd of 74 cows that had been free from tuberculosis for seven years 49 reactors suddenly appeared. Infection was traced to a woman milker who had assisted on the farm for a few weeks and was later discovered to be suffering from open pulmonary tuberculosis of the bovine type.

The part played by ruminants other than cattle and horses in spreading infection is less certain, since it is not known how far they are potential sources of danger to man. In all probability the horse, sheep, and goat can be disregarded on account of the relatively slight incidence of the disease.

Dogs and cats, however, which are in such intimate contact with man, may be responsible for the dissemination of infection. The public health aspect of tuberculosis in dogs and cats must receive much closer consideration. We may anticipate that with the progress in eradicating tuberculosis in cattle the disease should automatically become extinct in cats; but in the dog, on the other hand, the reduction of bovine infection will not influence the incidence of tuberculosis to the same extent. The predominant danger for the dog is the human being with an active pulmonary focus from which tubercle bacilli are disseminated in the sputum. For this reason it is important that, so far as is possible, the type of the bacillus responsible for canine cases should be typed.

Stableforth (1929) reported that in four out of six canine cases of tuberculosis there was a history of human infection. Herlitz (1939), carrying out an investigation on transmission of tuberculosis from dogs and cats to human beings, observed that only 13 out of 65 families who had owned tuberculous dogs were affected with tuberculosis. Evidence that infection had passed from animal to man was adjudged as probable in two cases only. Similar investigations were carried out by Hawthorne *et al.* (1957) in Glasgow. They examined not only animals living with tuberculous patients but also human beings living among tuberculous animals. They found nine significant cases of tuberculosis in 14 families living in contact with tuberculous dogs. The dogs and cats owned by 37 patients with active tuberculosis were examined for the isolation of *Myco. tuberculosis*. It was recovered from the alimentary tracts of two dogs and two cats.

In addition to these two large-scale investigations there are several small ones of sporadic cases of transmission of the disease from dogs or cats to man. Urwitz (1949) described five cases of tuberculosis in human beings all infected by one dog; De Kock and Le Roux (1956) recorded one case of tuberculosis contracted from a dog. Lewis-Jonsson (1946) described tuberculosis in a 3-year-old boy who was bitten on the forearm by a tuberculous cat. The wound started to heal, but after 23 days sores developed at one site of the bite. Further examination of the child revealed miliary tuberculosis in the lungs, and he died three and a half months after receiving the bite. These observations seem to indicate that tuberculosis in household animals must be regarded as a possible source of danger, and much more energy should be displayed in attempting to eliminate these cases and drawing attention to the risk of the dissemination of infection by dogs and cats. Unfortunately, at present very little can be done in preventing the spread of tuberculosis from the small animals to man. The following example illustrates the difficulty.

A cat was brought to the veterinary hospital for examination. On examination it showed the clinical picture of tuberculosis, confirmed by a strong positive tuberculin reaction. The owner of the cat was a mother of two children aged 2 and 6, and she was warned about the danger of having the animal in the house. She refused to allow the cat to be destroyed, and it was therefore handed back to her. This situation often occurs, particularly when the animal is a special pet of the family, and legally nothing can be done.

At present the control and prevention of animal diseases, so far as it affects the animal population, is vested in the Ministry of Agriculture and is under the direction of Government veterinary officers. But all questions referring to animal diseases in relation to human health are dealt with by the Ministry of Health in England and Wales and by the Department of Health for Scotland through local authorities. Neither of these health departments employs a veterinarian as an adviser on veterinary matters affecting public health in Great Britain, as is done in many countries on the Continent and in the United States. More and more stress is being placed on animal production; consequently as the density of the animal population increases the incidence of diseases transmissible from animals to man increases also. Therefore the medical and veterinary professions should work hand in hand.

However, let us hope and believe that tuberculosis in animals and man in this country will be reduced to a disease of minor importance, or perhaps to a disease of the past, such as pleuropneumonia in cattle and plague in man.

Perhaps I may fairly sum up by pointing to improvement of living conditions of man and animals as the most

important factor in the control of tuberculosis. Early diagnosis of the disease is of the utmost value. Mass radiography, substantially on a voluntary basis, is the medium in human medicine. Tuberculin-testing is the counterpart in the veterinary field, and voluntary measures are rapidly giving way to compulsion in relation to cattle. I think it is safe to say that the cattle of Britain will be free from this scourge before the people, but there will remain other animals to keep the disease alive in its various forms.

Summary

The proper study of tuberculosis among domestic animals started during the period of the industrial revolution, which played a great part in the increase of tuberculosis in man and animals, particularly in overcrowded towns. Although infection in both man and animals is via the respiratory tract and the alimentary canal, the lung and regional lymph-node lesions are not convincing evidence of aerogenous infection, as the tubercle bacillus can pass through the intestinal wall and localize in the pulmonary tissues without leaving any trace of its path.

Tuberculosis of cattle is nearly always caused by tubercle bacilli of bovine type; human and avian tubercle bacilli have rarely been found in cattle. At present, of the total of over ten million cattle in Great Britain, 73% are free of tuberculosis, and it is hoped that in the very near future tuberculosis will be completely eradicated from them. The part played by ruminants other than cattle and horses in spreading infection is slight, as they are rarely infected; but so long as only a few infected animals exist there will always be a hazard of infection.

Pigs are susceptible to human bovine and avian types of tubercle bacilli, but the bovine type is most common. The incidence of tuberculosis in pigs varies from 10 to 15%. The poor sanitary standard of slaughterhouses and the handling of meat and organs of tuberculous animals present a considerable risk of infection for meat inspectors and slaughterhouse employees.

Dogs and cats are a great risk in the dissemination of tuberculosis. At present there is no legislation by which a tuberculous dog or cat can be removed from the family. Therefore it is suggested that a veterinarian should be attached to the Ministry of Health in order to advise on the diseases transmitted from animals to man.

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INDOLIC COMPOUNDS IN THE URINE OF SCHIZOPHRENICS

BY

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It has been known for many years that certain drugs, such as harmine, ibogaine, hashish, and mescaline, were capable of giving rise to hallucinations in doses which were not dangerous to life and produced only minor physical effects. More recently the range of halucinants has been increased by the synthesis of lysergic acid diethylamide, medmain, adrenochrome, etc. These new drugs are much more active, and will give rise to a well-developed drug psychosis in doses not producing more than a very transient vasomotor or peripheral neurological discomfort. Osmond and Smythies (1952) and Hoffer *et al.* (1954) pointed out that all these drugs contained or could probably be easily converted into a chemical containing an indole nucleus. Woolley and Shaw (1954) also commented on the similarity of many of these substances to serotonin and on their ability to antagonize the action of serotonin on the arterial wall. On the other hand, most of these chemicals have another common factor—namely, an ethylamino or diethylamino side-chain directly attached to the benzene or pyrrole ring—so that the pharmacological evidence cannot unequivocally incriminate disordered indole metabolism as a cause of the hallucinations.

Turning to clinical evidence, Riegelhaupt (1956) found that there was an excess of a substance giving the glyoxylic reaction (Hopkins and Cole, 1901) in the urine of many more schizophrenics than in those patients suffering from other forms of mental disease. The glyoxylic reaction was at one time thought to be specific for tryptophan, but it is now known to be given by quite a number of chemicals containing an indole nucleus. For these reasons it seemed worth while to make a detailed study of the indolic compounds found in urines of schizophrenics and to compare them with those found in normal controls. This was made a practical possibility by the work of Dalgliesh (1955) and Jepson (1955). Their methods were combined and adapted in the following manner for the present investigation.

Experimental

From the first specimen of urine passed in the morning 200 ml. was collected. The creatinine was estimated by the method of King and Wootton (1956) and a concentrate made by the technique described by Dalgliesh (1955), except that the carbon was blocked with 8% *n*-octadecylamine. During the steam distillation under reduced pressure the temperature was not allowed to rise above 65° C., since higher temperatures made the semi-quantitative results less repeatable. This was particularly noticeable with indole compounds substituted in the benzene ring. The final concentrate was dissolved in 50% v/v mixture of isopropyl alcohol and water. The volume of this solvent was so arranged that the aromatic substances recovered from a volume of urine containing 100 mg. of creatinine were present in 1 ml. of the final concentrate. This concentrate does not keep for long without decomposition, even at −15° C., and so it was applied as soon as possible to sheets of Whatman's 3 MM filter paper 34 by 32 cm. The volume

used was such that the equivalent of 2 mg. of creatinine was represented in the "spot," which was kept less than 0.7 cm. in diameter.

The "spotting" was carried out at room temperature without air blast or heat, both of which procedures were found to detract from the accuracy of the results. The papers were transferred to all-glass chromatograph tanks. The first dimension was run in a mixture of isopropyl alcohol 100 parts, water 10 parts, and ammonia (sp. gr. 880) 10 parts at room temperature for 18 hours. The papers were dried in an oven maintained at 40° C. and, as soon as they were dry, transferred to a refrigerator, where they were kept until the evening, when they were run in the second dimension in *n*-butyl alcohol 600 parts, acetic acid 200 parts, and water 250 parts. Again the run was overnight (usually 16 hours) in a refrigerator which maintained a temperature between 0 and 4° C., the runs in each case being in the ascending direction without equilibration. The papers were dried as before and immediately sprayed with Ehrlich's reagent (1% solution of *p*-dimethyl-aminobenzaldehyde) in 2N HCl. The papers were hung at room temperature for exactly three hours and the maximum density of the "spots" was read without the use of a colour filter on a photoelectric densitometer, the galvanometer of which was provided with a logarithmic scale.

Although this technique cannot be used at all easily to measure the actual quantity of the indoles present, it is a very satisfactory method of comparing the amounts of indolic substance present in a number of specimens, since it gives both consistent and reproducible results. In artificial mixtures of indolic compounds, in normal urine, and in urines to which indolic compounds have been added, the density of the "spot" bears a fixed non-linear relation to the amount of the substance present in the original specimen.

After much preliminary work it was decided to investigate in detail seven well-defined spots which occurred fairly consistently on the chromatograms made from the urinary concentrates of schizophrenics. The chemicals causing five of these spots are known beyond reasonable doubt; they are tryptophan, indolyl acetic acid, 5-hydroxy-indolyl acetic acid, indolyl acetyl glutamine, and potassium indoxyl sulphate. One of the other two has been provisionally identified as potassium skatoxyl sulphate, since a substance with exactly similar chromatographic properties can be obtained from an alkaline persulphate oxidation of skatol; nevertheless this will be referred to as spot "Q." It has an R_f of 0.79 in the isopropyl alcohol solvent and of 0.43 in the *n*-butyl alcohol solvent. The other substance will be referred to as spot "S." It has R_f values of 0.31 and 0.44 respectively in the two solvents. With Ehrlich's reagent it gives a blue-violet colour, which appears rapidly and fades only slowly. Hydrolysation of the urine has no effect on the depth of the spot. It does not stain with diazotized I.C.I. 5901 ("Boscott's reagent," Boscott and Cooke, 1954) nor with 1-nitroso-2-naphthol. These reactions suggest that, while the substance causing this spot almost certainly contains an indole nucleus, it is not a 5-hydroxy derivative of tryptophan. These seven spots were by no means all those on the chromatograms of the urine concentrates that were observed to stain with Ehrlich's reagent in a manner suggestive of an indole compound, but they were the most constant and discrete observed.

Selection of Patients and Controls

Fifty "confirmed" schizophrenic patients between the ages of 19 and 40 were selected from a much larger number of possible examples in the wards of Hollymoor and Rubery Hill Hospitals. All conformed to the following criteria: (1) They had been in hospital long enough for their notes to show that they suffered from at least four of the following symptoms, considered by many psychiatrists to be typical of schizophrenia: "thought disorder, withdrawal of interest from surroundings, hallucinations, retardation, incongruity of affect, attitude of suspicion, delusions, disorientation, morbid introspection." (2) They had all been diagnosed as schizophrenics by the consultant psychiatrist in charge of the ward in which they were during the period of this investigation. (3) They were either not receiving active treatment or could be taken off treatment for the period of the investigation.

There were 28 males and 22 females, and their average age was 27 years. Fig. 1 shows the length of time symptoms had been present and the number of patients in each group.

The controls consisted of members of the nursing staff of the two hospitals. Their average age was 31 years, and there were 23 males and 27 females. The male–female ratio in the controls is slightly lower than in the group of patients, but this is not regarded as important, since no difference between the results for the two sexes could be detected in either group.

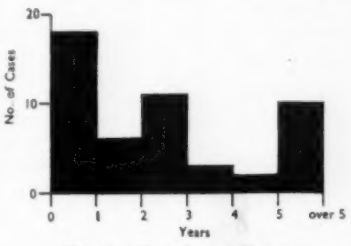

FIG. 1.—Duration of illness.

Although it is not considered likely that small variation in diet affects appreciably the substances being investigated, an effort to eliminate this possible source of error was made by collecting the urine of the controls and patients after they had received similar diets. It was not found possible to prevent the patients having any drugs at all, since barbiturates and other hypnotics are often essential. No patient who had received treatment recently with any of the tranquillizers was included in the investigation. The concentrates from the patients and controls were made and the chromatograms run alternately whenever possible in order to minimize the effect of day-to-day variations in conditions and technique.

Results

Figs. 2 to 8 show the results in diagrammatic form. The densitometer readings for this purpose are shown in 10-unit grouping.

From Fig. 2, which portrays the excretion of 5-hydroxy-indolyl acetic acid, it is obvious that there is a considerable difference in the distributions as between the control group and the schizophrenics. None of the control group shows a densitometer reading below 10, while 11 out of 50 of the schizophrenics gave this result. There is also more scatter for the readings of the schizophrenics, there being about an equal number of cases in each group from 0 to 40, while more than half the normal controls fall between 20 and 30. Fig. 3 shows the excretion of the substance designated as spot S. The diagram demonstrates clearly that the schizophrenics excrete much more of this substance than do the controls. Almost three-fifths of the controls have a reading of less than 10, while four-fifths of the schizophrenics have a reading of 10 or more. Fig. 4 shows the results for spot Q (which may well be potassium skatoxyl sulphate). Here again the schizophrenic group excrete more than the control group, but the difference is somewhat less striking.

Figs. 5, 6, 7, and 8 show the excretion of tryptophan, indolyl acetic acid, potassium indoxyl sulphate, and indolyl acetyl glutamine respectively. For these substances not only is there no outstanding difference between the two groups but the pattern of excretion is moderately similar. It is noteworthy that the results for potassium indoxyl sulphate are not higher for the schizophrenics than for the normal controls.

Table I shows these results analysed both by the standard error of the differences between the means and by the χ^2 test (using a 2 by 3 or 2 by 4 table after grouping, so that the expected result for any cell is not less than 5) on the overall distribution of results set out in Figs. 2 to 8.

An examination of Table I shows that the numerical results confirm the impression gained from the diagrams. For spot S the difference between the normals and schizophrenics is highly significant. For 5-hydroxy-indolyl acetic acid and for spot Q the differences exceed the accepted levels of "significance" ($P<0.05$) as judged by one or other of the tests. The similarity of the control group and the schizophrenics for the other four substances already demonstrated in the diagrams is supported by the analysis in Table I.

TABLE I

Substance	Control Mean	Schizophrenic Mean	S.E. of Difference	P	χ^2	P
5-Hydroxy-indolyl acetic acid ..	26·7	22·9	2·15	0·1	7·9	0·05
Spot S	9·5	22·0	2·3	0·001	12·6	0·01
,, Q	19·1	29·0	3·37	0·01	6·6	0·1
Tryptophan ..	30·4	28·9	3·19	0·6	2·25	0·5
Indolyl acetic acid	24·3	25·7	2·64	0·6	1·67	0·3
Potassium indoxyl sulphate ..	29·6	27·6	2·23	0·3	0·59	0·8
Indolyl acetyl glutamine ..	30·0	28·1	2·85	0·4	1·22	0·7

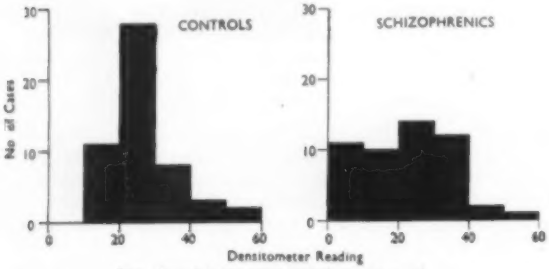

FIG. 2.—5-hydroxy-indolyl acetic acid.

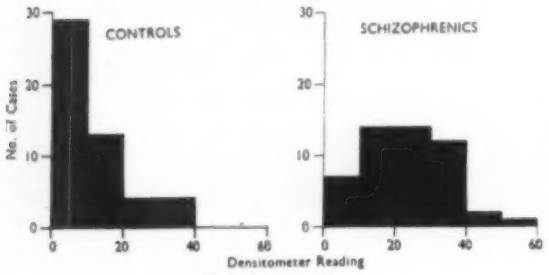

FIG. 3.—Spot S.

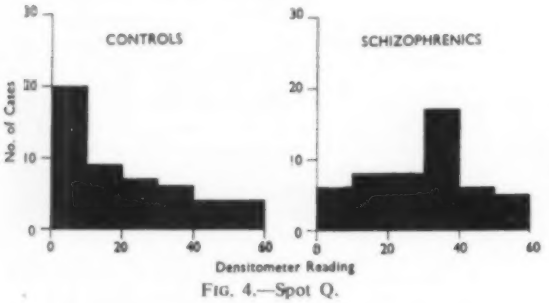

FIG. 4.—Spot Q.

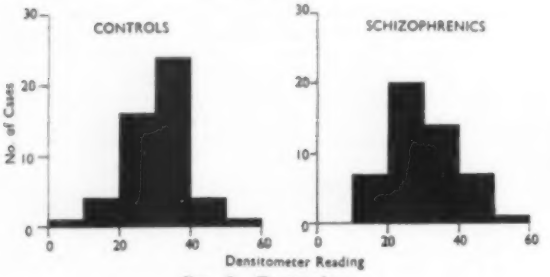

FIG. 5.—Tryptophan.

Consistency of Results

The results so far described were obtained from single specimens of urine. It seemed important to find out whether some of the patients who showed an abnormal pattern of excretion of indole metabolites maintained this abnormality

TABLE II.—*Densitometer Readings*

Patient	Specimen 1st	2nd	3rd	4th	5th	Mean	S.D.
5-Hydroxy-indolyl-3-acetic acid. Normal mean, 26·7. Standard deviation, 9·2							
TU	11	7	6	11	10	9·0	2·1
JA	9	12	8	6	10	9·0	2·1
DI	6	8	7	9	8	7·6	1·0
MA	8	9	6	10	7	8·0	1·1
JM	8	11	6	12	10	9·4	2·1
Spot S. Normal mean, 9·5. Standard deviation, 10·6							
JA	34	33	40	46	37	38·0	4·6
DI	16	23	29	30	22	24·0	5·1
MA	34	33	40	40	47	38·8	4·7
LO	32	36	42	34	30	33·6	4·4
SI	47	37	43	30	41	39·6	5·8
Spot Q. Normal mean, 19·06. Standard deviation, 17·6							
JA	9	10	15	12	16	12·2	2·7
DI	33	40	31	42	33	35·8	4·3
MA	31	42	30	46	37	37·2	6·2
LO	34	37	30	43	33	35·2	4·5
SI	57	46	37	43	32	43·0	8·5

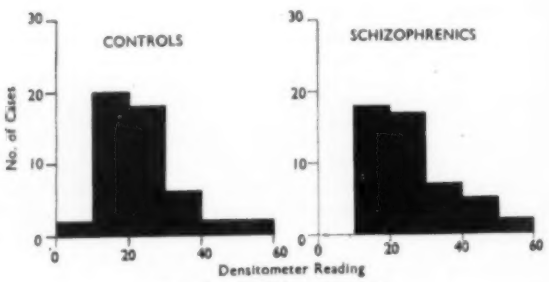

FIG. 6.—Indolyl acetic acid.

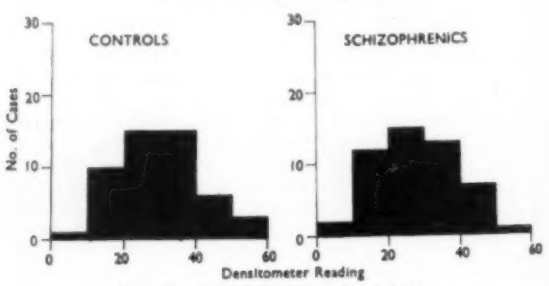

FIG. 7.—Potassium indoxyl sulphate.

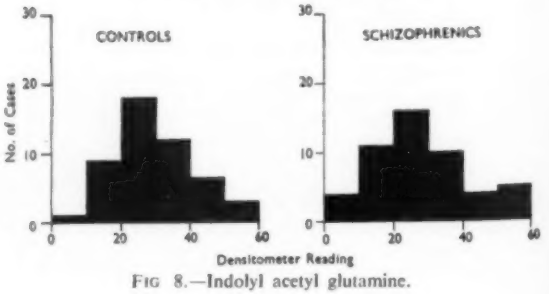

FIG. 8.—Indolyl acetyl glutamine.

over a considerable period of time. To test this the urine of seven patients was examined on five occasions at approximately fortnightly intervals. Table II shows the results.

These patients were selected because they showed at least two of the three major abnormalities described. Table II shows clearly that during the two and a half months during which specimens were collected there was little change in the level of excretion of the three indolic substances examined. When they were abnormal to begin with they remained outside the normal range and the portion that was normal remained within the normal range. It is quite possible that part of the variation shown in Table II is due to the inherent error in the technique of the estimations, and if this be the case it is probable that the abnormal pattern of excretion of these indole compounds remains even more constant.

Discussion

In attempting to assess the results described it is important to remember two facts. In recent years there has been a growing tendency for schizophrenia to be regarded as a syndrome rather than a single disease. This has made it much more difficult for the investigator interested in any biochemical changes which might be present in schizophrenics, since even if the patients are selected by a group of psychiatrists it is unlikely that they will all be suffering from exactly the same disease, although they may present many of the same symptoms. This difficulty in the choice of patients makes it unlikely that every member of a schizophrenic group would show the same metabolic abnormality.

Also, the chemical technique employed, while capable of demonstrating minute quantities of indole compounds, is only semiquantitative. It follows that small real differences between individual schizophrenic patients and normals could well have been overlooked in the present investigation, although it is realized that they might be important; but in the case of three of the compounds estimated there are major differences to be considered. For the spots S and Q it appears that the majority of schizophrenics excrete more of these substances than the normal. For 5-hydroxy-indolyl acetic acid a proportion in the order of 20% excrete much less than normal. It is realized that the controls in the present series are such as only to show a difference between normals and schizophrenics. It is possible that the differences demonstrated might merely be an association with living in a mental hospital, or might occur equally often in other types of mental diseases, although the work of Riegelhaupt (1956), who used mentally deranged patients who were not schizophrenics for his controls, makes this unlikely. So far it has not been possible to show any correlation between the abnormalities described, so they must be considered separately.

The group of schizophrenics which has a decreased output of 5-hydroxy-indolyl acetic acid is of special interest because a considerable amount is known about how this final metabolite is produced. It is almost certain that tryptophan is hydroxylated to 5-hydroxy-tryptophan in the argentophil cells of the intestine and probably released into the blood stream (Dalgleish and Dutton, 1957; Smith *et al.*, 1957). Where it is decarboxylated into 5-hydroxy-tryptamine (serotonin) is not certain, since 5-hydroxy-tryptophan decarboxylase is widely distributed throughout the body (Gaddum and Giarman, 1956). It is certain that the platelets and certain portions of the brain contain much more 5-hydroxy-tryptamine than most other body tissues (Udenfriend *et al.*, 1955, 1956). Although there is little proof, it is a reasonable assumption that the 5-hydroxy-indolyl acetic acid in the urine is the final oxidation product of 5-hydroxy-tryptamine. It is known that 5-hydroxy-tryptamine is physiologically an extremely active substance; some of its antagonists if given to man give rise to mental aberrations (Woolley and Shaw, 1954), while 5-hydroxy-tryptamine itself if given into the ventricles of the brain gives temporary improvement in cases of schizophrenia (Sherwood, 1955). Unless there is an abnormal deviation from the usual metabolic pathway the deficiency in the excretion of 5-hydroxy-indolyl acetic acid must be attributed to a lack of the ability to synthesize enough 5-hydroxy-tryptophan. This hypothesis is supported by the fact that by giving 5-hydroxy-DL-tryptophan by mouth it has been found possible, in trials to be described separately, to raise the excretion of 5-hydroxy-indolyl acetic acid of some patients whose urinary excretion of this substance was below normal. Whether this procedure, by which the biochemical abnormality present can be corrected, will be of any value in treatment is still under investigation.

Little can be said about the increase in spots S and Q, as their chemical constitution is not known for certain. Since the amount of potassium indoxyl sulphate excreted is not increased in the schizophrenic group it is very unlikely that bacterial degradation of tryptophan in the intestine plays any part in the finding of excessive quantities of substances S and Q in the urine. Their presence strengthens the case for further investigation into the tryptophan metabolism in schizophrenics.

For the present the difference in depths of spots S and Q between schizophrenics and controls may be of some assistance in the diagnosis of early or obscure cases of schizophrenia. The low level of excretion of 5-hydroxy-indolyl acetic acid would not appear to be suitable for development as a specific test for schizophrenia, since similar findings have been reported in other mental diseases—for example, untreated phenylketonuria (Pare *et al.*, 1957), but it might turn out to be of use to segregate on biochemical lines about 20% of schizophrenics from the remaining 80%. This would be particularly valuable if it were found possible to correlate this biochemical abnormality with other differences in symptoms and prognosis.

Summary

The level of excretion of seven indolic substances found in the urine of schizophrenics is compared with that found in a similar number of normal people. It is found that about 20% of schizophrenics excrete less 5-hydroxy-indolyl acetic acid than any among the control group. Two other substances which probably contain the indole nucleus are excreted in significantly larger quantities by the schizophrenics than by the group of normals.

The significance of the low excretion of 5-hydroxy-indolyl acetic acid is discussed, its possible value as a beginning of a biochemical classification of schizophrenia suggested, and the treatment of certain cases with 5-hydroxy-tryptophan considered.

The possibility of using the excess excretion of the other two indolic substances as an aid to the diagnosis of schizophrenia is mooted.

I thank the medical staff of both Hollymoor and Rubery Hill hospitals for their co-operation and for access to their patients; Professor J. R. Squire for his help and encouragement in the preparation of this paper; Dr. J. B. Jepson for a gift of indolyl acetyl glutamine; Messrs. Upjohn Ltd. for a generous supply of 5-hydroxy-indolyl acetic acid; and Roche Products Ltd. for an authentic sample of 5-hydroxy-tryptophan.

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CLINICAL COMPARISON OF METHYPRYLONE AND QUINALBARBITONE AS HYPNOTICS

SEQUENTIAL ANALYSIS USED

BY

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Methyprylone ("noludar"; 2,4-dioxo-3,3-diethyl-5-methyl-piperidine) is a non-barbiturate hypnotic. Stewart (1956) reported that in a dose of 200 mg. it had a hypnotic effect comparable to 100 mg. of either amylobarbitone sodium or butobarbitone. Lasagna (1956) found that 250 mg. of methyprylone produced results "essentially indistinguishable" from those of 100 mg. of pentobarbitone or 100 mg. of quinalbarbitone.

The purpose of the present investigation was to compare the hypnotic effects of methyprylone and standard doses of quinalbarbitone; ascorbic acid was used as a control.

Method

The patients were in general medical wards and presented a wide variety of diagnoses; there were 92 men and 36 women, and their ages ranged from 24 to 74 years. Only those who required hypnotic drugs were included in the trials. All other sedatives were withdrawn during the period of observation. The plan was similar in each of the four clinical trials. The two drugs to be compared were dispensed as white powders of similar bulk, labelled A or B, their content being unknown to patient, nurse, or clinician.

The Table lists the contents of the powders used in the four trials. If powder A was given on the first night, powder B was ordered on the second, and vice versa. To avoid bias, the order of giving powder A or B on the first of the two test nights was decided by random selection; after mixing 20 labels marked A and 20 of B, the order in which they were then drawn from a box was listed, and this determined the order of administration. When it was found during a trial that more than 40 patients were required to complete the study (51 in trial 1 and 67 in trial 3), a further list of 40 was compiled by the same method of random selection. The appropriate powder was given with a small draught of water at 10 p.m. Each patient was informed that he was receiving "a sleeping powder"; he was not told that a comparative study was in progress. The nurse was asked to observe the patient during the night and record her opinion of the soundness of sleep in the following terms: "good," "intermediate," or "poor." In the morning after the second hypnotic I asked each patient, "On which of the two nights did you have the better sleep?" Care was taken to use the same form of words, with the deliberate intention of eliciting a comparison.

Content of Powders A and B in the Trials

Trial No.	A	B
1	200 mg. ascorbic acid	200 mg. methyprylone
2	400 ,, methyprylone	400 ,, ascorbic acid
3	400 ,, ,,	200 ,, quinalbarbitone + 200 mg. ascorbic acid
4	400 ,, ,,	100 mg. quinalbarbitone + 300 mg. ascorbic acid

The results were examined statistically by the method of sequential analysis as described by Bross (1952), and the original paper should be consulted for a detailed explanation of the statistical significance of this sequential plan. The outstanding feature of this method is that observations are charted as soon as they become available. Looking at Fig. 1 as an example, only a stated preference between A and B is plotted as X; if a patient states that there is "no difference" between the treatments, no entry is made on the chart. If the patient states a preference for A, a mark X is placed in the square to the right of the last entry on the chart; if the preference is for B, the mark is placed in the square above the last entry. When the path of these symbols travels "north" and emerges from the boxed area, "B treatment" is superior; if beyond the "eastern" barrier, "A treatment" is superior. If the data as plotted fall into the zone between the two boxed areas, this denotes "no important difference between treatments." The clinical trial—to compare A and B—ends when the X path crosses any boundary of the boxed areas.

Results

The results are shown in Figs. 1–4, which should be read in conjunction with the Table. The first trial demonstrated no important difference between 200 mg. of methyprylone

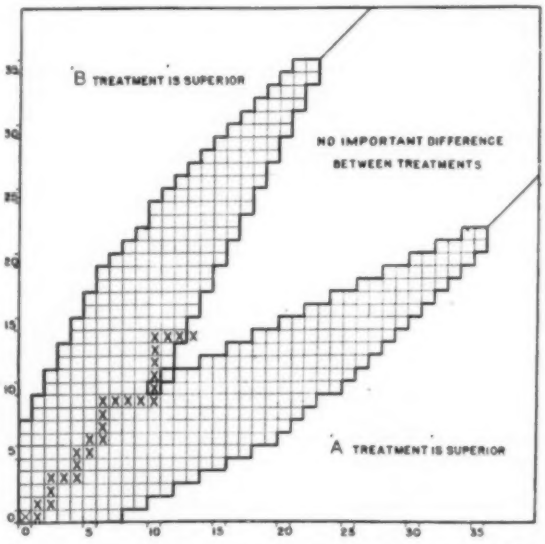

FIG. 1.—Sequential plan in trial 1, showing no important difference between the "treatments."

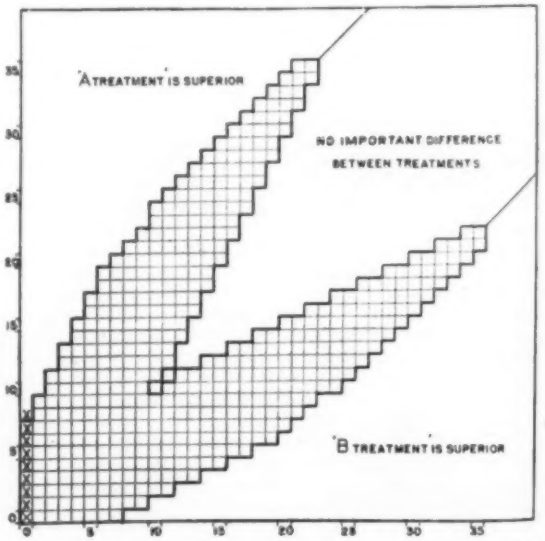

FIG. 2.—Trial 2, in which "A treatment" was superior to "B treatment."

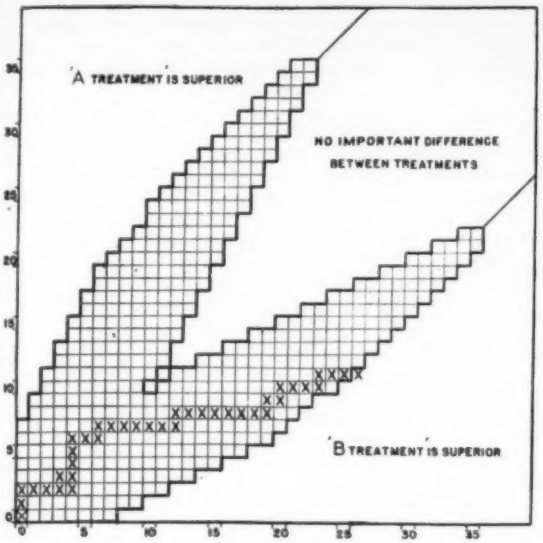

FIG. 3.—Trial 3, showing 200 mg. of quinalbarbitone to be superior to 400 mg. of methyprylone.

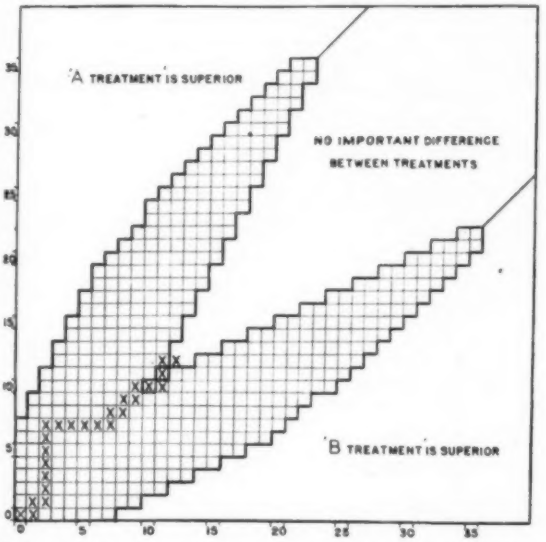

FIG. 4.—Trial 4, in which there was no important difference between 100 mg. of quinalbarbitone and 400 mg. of methyprylone.

and 200 mg. of ascorbic acid as hypnotics. To reach this conclusion 51 patients were studied, of whom 24 stated there was "no difference" between the drugs. The second trial (Fig. 2) showed that 400 mg. of methyprylone was superior as a hypnotic to 400 mg. of ascorbic acid. This study required only 12 patients, as 8 stated a preference for powder A, and 4 "no difference" results were obtained. Trials 3 and 4 were planned to allow a comparison to be made of the hypnotic effect of 400 mg. of methyprylone with the hypnotic effect of quinalbarbitone in the commonly prescribed doses of 100 or 200 mg. The results (Fig. 3) indicated that 200 mg. of quinalbarbitone was superior to 400 mg. of methyprylone; the "eastern" boundary was crossed after 37 preferences and there were 30 "no difference" results. When the hypnotic effect of 400 mg. of methyprylone was compared with that of 100 mg. of quinalbarbitone, no important difference was found; this trial required 40 patients, 16 of whom found "no difference" between the drugs.

Discussion

There are many factors which can be considered while comparing the therapeutic value of two hypnotic drugs. The present trials have not sought to define the time of onset of hypnotic action, or its duration, the presence of disturbing dreams, or toxic effects. In this study, only the patient's judgment of the quality of sleep after different hypnotics has been used. It is interesting to note, however, that the data obtained during these clinical trials also permit of some comment on the degree of correlation existing between a clinician's assessment and that of the nurse. When the preferences for the sequential analysis were based on the nurses' considered opinions, the paths travelled in the same directions as in Figs. 1–4, but more slowly. The latter was due to the greater number of "no difference" results offered by the nurses.

Summary

The hypnotic effect of methyprylone (noludar) has been compared with the hypnotic effect of quinalbarbitone, using the double-blind technique. Powders of ascorbic acid were used as a control. The results were assessed by sequential analysis.

No important difference could be detected between the apparent hypnotic action of 200 mg. of methyprylone and the control powder. When the hypnotic effects of 400 mg. of methyprylone and 100 mg. of quinalbarbitone were compared no important difference was discovered.

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RATIONALE OF ANTIHISTAMINIC THERAPY IN THERMAL INJURY

AN EXPERIMENTAL EVALUATION IN THE GUINEA-PIG

BY

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Clinical trials with antihistamines in the *early* treatment of burns suggest that these drugs, applied locally or given orally, are useful in combating pain, blistering, oedema, and infection, and consequently in accelerating healing (see correspondence in the *British Medical Journal*, cited by Sevitt, Bull, Cruickshank, Jackson, and Lowbury, 1952). This clinical finding is consistent with Lewis's (1927) observation that the triple response elicited by pricking histamine into human skin is also induced by thermal injury, and with the fact that histamine is readily released *in vitro* by heat from the skin of various species of animal (Rosenthal and Minard, 1939). However, in human volunteers given an oral antihistamine immediately after experimental burns were made, Sevitt *et al.* (1952) could not confirm the clinical findings; and the increased vascular permeability induced by high-temperature burns in rabbits (Weeks and Gunnar, 1949) and by thermal injury in anaesthetized guinea-pigs (Sevitt, 1949) is not antagonized by high doses of antihistamines. Evidence of this kind from the rabbit and guinea-pig must be given

considerable weight because in each animal histamine has the same high order of permeability-increasing potency as it has in man (Miles and Wilhelm, 1958a).

In re-examining the possible role of histamine in thermal injury, we investigated the response in guinea-pig skin to a *minimal* injury that consistently induced a substantial increase of vascular permeability. A minimal injury avoids two factors that possibly complicated the interpretation of the work of Weeks and Gunnar (1949) and of Sevitt (1949): firstly, the pharmacological picture is less likely to be complicated by non-specific breakdown products that almost certainly appear after high-temperature injury; and, secondly, since the stimulus is not painful, it permits the investigation to be made in unanaesthetized animals, thus avoiding the depression which anaesthesia induces in the permeability response of the peripheral vessels (Miles and Miles, 1952).

After establishing the maximal tolerable stimulus first on ourselves and then on guinea-pigs, thermal injury was induced by applying a copper disk, 9 mm. in diameter, maintained at a temperature of 54° C. by flowing water at a constant temperature, to the depilated skin of the back of the trunk of guinea-pigs for periods up to 30 seconds. This degree of heat stimulus is so mild that it can be applied to completely unrestrained animals without their moving away from the disk. The animals, 650–750 g., were previously given intravenous pontamine blue, 50 mg./kg. Such animals are referred to as "blued." Increased vascular permeability at the heated sites, indicated by the local exudation of the blue dye, was graded −, ±, +, +±, ++, up to ++++; ± represents the faintest trace, and ++++ an intense dark blue.

We found at heated skin sites two distinct permeability responses: an immediate response, best elicited by five seconds' heating, which appears in less than one minute, and is almost certainly mediated by liberated histamine; and a delayed response, which appears one hour after 20 seconds' heating and which is apparently not induced by histamine, or in any way dependent on the magnitude of the immediate response to liberated histamine which precedes it.

The Immediate Response

Skin sites heated at 54° C. for five seconds become erythematous in 30–40 seconds, and blue after a further 5–10 seconds; the blueing is maximal (++ to +++) in five minutes (Fig. 1). Tested by the technique of Miles and Miles (1952), the permeability of the blood vessels in the heated skin returns to its normal low level in 10 minutes (Fig. 2, A). The heated skin neither blisters nor becomes necrotic.

This immediate response is highly susceptible to antihistamines previously injected locally into the skin or given intravenously. In our hands the preferred antihistamine in guinea-pigs (Mason and Wilhelm, to be published) is triprolidine ("actidil," see Green, 1953). The prior *intracutaneous* injection of 2 μg. of triprolidine base in 0.1 ml. of saline into the test site consistently decreases responses of ++ to +++ to less than ±, and even 0.02 μg. has a substantial effect (Fig. 1). However, the application immediately after heating of lint squares soaked in a 1% solution of triprolidine does not affect the response. Thermal lesions were also compared in the same animal before and after the *intravenous* injection of triprolidine. Intravenous triprolidine antagonized the immediate response even more effectively than intracutaneous; doses of 100 μg./kg. decreased responses of ++ to +++ to less than ±, and of as little as 10 μg./kg. to ± (Fig. 1).

In unblued guinea-pigs, slight oedema of the heated skin corresponded in onset and development with local blueing in blued animals, and had the same susceptibility as local blueing to intravenous triprolidine. Erythema, however, was not affected by triprolidine.

Eight other antihistamines, in intravenous doses of 1 mg./kg., each substantially antagonized the immediate response in blued animals; but in doses of 0.1 mg./kg. they decreased the response in the following descending order of potency: triprolidine, mepyramine, chlorprophenpyridamine, tripelennamine, promethazine, diphenhydramine, chlorcyclizine, thenalidine, and antazoline, the last two having only a slight effect. These drugs are effective in practically the same order as inhibitors of the permeability increase induced by intracutaneous histamine and by the histamine-liberator 48/80.

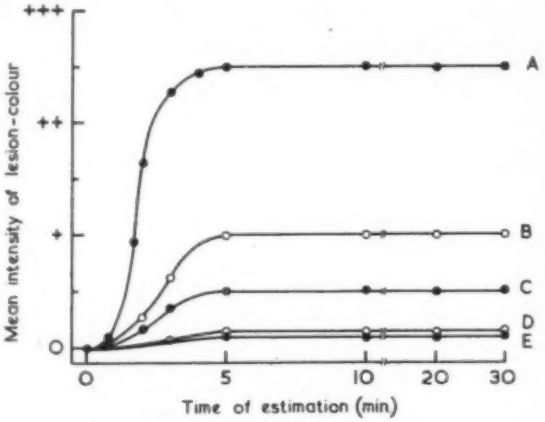

FIG. 1.—Maturation of the immediate permeability effect in the blued guinea-pig during the 30 minutes following a mild heat stimulus to the skin (A); and the influence of prior treatment with the antihistamine triprolidine, 0.02 μg. (B) and 2 μg. (D) intracutaneously, and 10 μg./kg. (C) and 100 μg./kg. (E) intravenously.

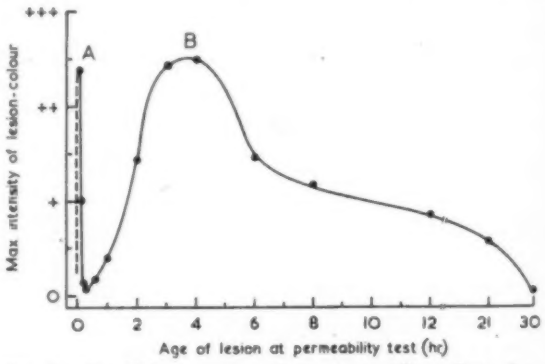

FIG. 2.—The diphasic nature of the permeability effect of a moderate heat stimulus in the skin of the guinea-pig.

The high susceptibility of the immediate response to small doses of antihistamines suggests that only small amounts of histamine are liberated. This is supported by the low histamine content that we found in intercellular perfusates (Miles and Wilhelm, 1958b) from skin strips, 10 by 30 mm., which had been heated *in vivo* (0.015–0.03 μg. of histamine per heated strip, compared with <0.007 μg. per control strip). Furthermore, when finely chopped and washed skin from normal animals was heated in Locke's solution at 54° C. for five seconds to five minutes, the Locke's solution contained only 1–5% of the histamine liberated by heating at 95–100° C. for five minutes (cf. Rosenthal, Samet, Winzler, and Shkolnik, 1957). Skin, in pieces 5 by 5 mm., heated at 98° C. for five minutes yielded only 20% of its

histamine (cf. Rosenthal *et al.*, 1957). All the liberatable histamine was, in fact, released at this temperature, because when this heated skin was finely chopped the remaining 80% readily leached into the suspending fluid.

The Delayed Response

Sevitt (1958) records that, in anaesthetized guinea-pigs, heating at 60° C. for 10 seconds induces substantial local oedema maximal eight hours after injury. We induced a similar delayed response in our unanaesthetized animals by heating for 20 seconds at 54° C. The immediate response was now minimal, being represented by only a thin ring of blueing not more than 1 mm. wide at the periphery of the heated site; and, like that to 54° C. for five seconds, it was abolished by prior antihistamine treatment. However, after a half to one hour, additional blueing appeared within the peripheral ring of colour, and the entire lesion became evenly blued (++ to +++) during the next two to three hours. This delayed response is illustrated by the experiment recorded in Fig. 2, B, in which intravenous dye was given to animals bearing lesions from one minute to 30 hours old.

In anaesthetized animals, heating at 58° C. for 10–20 seconds hastened the development of the delayed response; but, even so, central blueing did not appear until the lesions were 5–10 minutes old, and took 60–90 minutes to mature.

We were unable to identify the permeability factor mediating the delayed response. Intravenous triprolidine, 0.1–1 mg./kg., given before or during the development of the lesions, did not affect the response; and inhibitors of the globulin permeability factor in guinea-pig serum and tissue fluid of the skin (Miles and Wilhelm, 1955, 1958b; Wilhelm, Miles, and Mackay, 1955) were also ineffective.

The serum-globulin permeability factor in the guinea-pig, as well as in other species, including man (Mill, Elder, Miles, and Wilhelm, 1958), is a protease that is highly susceptible to soya bean trypsin inhibitor (S.B.T.I.) and to the esterase inhibitor di-*iso*propyl fluorophosphonate (D.F.P.; see Becker, 1958; Miles and Wilhelm, 1958a). Injected locally into the skin, both before and during the development of the delayed response, relatively large doses of S.B.T.I. and of D.F.P. each failed to affect the response. Intravenous S.B.T.I. also was ineffective; and, contrary to Spector and Willoughby's (1958) finding in the rat, intraperitoneal D.F.P. in our guinea-pigs induced only a non-specific depression of the vascular responsiveness. The immediate response was also insusceptible to local S.B.T.I. and D.F.P.

Summary and Conclusions

Mild heat treatment of the skin of the guinea-pig is followed by an immediate and short-lived increase in vascular permeability, which is mediated by histamine. With moderate heat treatment the immediate response is followed by a delayed and more prolonged response, which, so far as our evidence goes, is mediated neither by histamine nor by other recognized endogenous permeability factors.

If it is justifiable to generalize from the guinea-pig to man, then we expect a substantial liberation of effective histamine only in the very mild burn with no ostensible damage to or rupture of the skin; and little or none in moderate or severe burns, owing to changes in the tissues that either inhibit histamine liberation, restrain the movement of liberated histamine to susceptible blood vessels, or otherwise alter the capacity of the vessels to manifest a permeability effect.

Since the histamine effect lasts only 10 minutes, in any efficient treatment of mild burns by an antihistamine, the drug would have to be applied within a few minutes, either locally in a form capable of rapid penetration of unbroken skin or intravenously. Moreover, since the intensity of the delayed vascular response we observed was not diminished when the early histamine effect was neutralized, the antihistamine would do nothing to inhibit these delayed effects, even supposing the burn were severe enough to induce them.

It is possible, however, that histamine liberated and held in the tissue of more severe burns might later be released to the detriment of surrounding tissues and consequently that prophylactic antihistamine might diminish later deleterious responses to the injury. An *in vivo* experimental proof of such an action in severe burns was beyond the scope of this investigation.

As regards the delayed permeability response, the time relation of which is similar to that induced in the guinea-pig by bacterial infection (Burke and Miles, 1958) and certain bacterial toxins (Elder and Miles, 1957), we have as yet no evidence of the nature of the mediating factor and can offer no rationale for its treatment.

We are indebted to Allen and Hanburys Ltd., London; Ciba Laboratories, Horsham; May and Baker Ltd., Dagenham; Parke, Davis and Co. Ltd., London; Sandoz Products Ltd., London; and the Wellcome Research Laboratories, Beckenham, for supplies of antihistamines; and to the Nuffield Trust for financial help in the prosecution of this work.

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Minds Matter: A New Approach to Mental Health is the title of a 62-page booklet published by the Conservative Political Centre on behalf of the "Bow Group." The author, Miss BERYL COOPER, is a 30-year-old Birmingham graduate who is stated to have worked for seven years in the Hospital Service, three of them "as hospital secretary at a teaching hospital in London." After an introductory chapter on the extent of the present problem, Miss Cooper discusses in turn past and present legislation on the care of the mentally ill, the Royal Commission's report, local responsibilities and voluntary sources of help, costs and staffing, the administrative structure, and community services. She ends with a "four-point plan for mental health": (1) Certification to be abolished, with admission to mental hospitals to be voluntary whenever possible and with a procedure as simple as with general hospitals. (2) Most patients to be treated at home so that they do not become cut off from the community. (3) Hostels for milder cases and the old, training-schools for the younger, and more "day" and "night" hospitals to be built. (4) 138 new committees to take over hospital administration now shared between 14 regional boards and 400 management committees, and be financed by five-yearly direct Government grants.

HYPOTHERMIC MYXOEDEMA COMA

THREE CASE REPORTS

BY

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Hypothermic myxoedema coma is an uncommon condition in which interest has grown recently (*Lancet*, 1956). Only 15 cases have been reported, and those since 1953. Three further cases are reported, each of interest in itself. Case 1 is the first reported case of hypothermic coma in juvenile myxoedema. Case 2 is the oldest reported case. Case 3 is the second reported case to have survived over three months.

Case 1

A youth aged 19 was admitted to hospital in coma on November 21, 1956. At the age of 12 he developed weakness of his legs, and from that time his walking deteriorated, although he remained mentally alert. During the 12 months before admission he became increasingly lethargic, spending most of his time asleep before the fire. On the day of admission he could not be roused.

On examination he was deeply unconscious. Physically he had the appearance of a boy of 12. His skin was soft, dry, and cold; his lips were thick and a large tongue protruded from his mouth. Axillary and pubic hair were present. His genitalia showed normal development. The rectal temperature was 82° F. (27.8° C.); the apex rate 50 a minute; respiratory rate 2 a minute; B.P. 80/60 mm. Hg.

Investigations.—Hb, 98%; W.B.C., 19,000/c.mm., mainly polymorphs; blood cholesterol, 200 mg./100 ml.; serum sodium, 144 mEq/l.; serum potassium, 6.7 mEq/l.; plasma chlorides, 63 mEq/l.; CO_2 combining power, 41 mm./l.; blood sugar, 100 mg./100 ml. E.C.G. twelve hours after admission showed low-voltage complexes in all leads in sinus rhythm at 100/minute. *X*-ray examination of the chest was negative.

Treatment was begun immediately: (1) Warmth:—He was immersed in a lukewarm bath until the rectal temperature rose to 89° F. (31.7° C.), and then nursed between electric blankets until his temperature reached 95° F. (35° C.), eight hours after admission. He was then maintained at this level by intermittent heating from the electric blankets. (2) L-thyroxine sodium, 0.02 mg. four-hourly, was given sublingually. (3) Cortisone:—100 mg. of hydrocortisone hemisuccinate was given intravenously over the first 12 hours, then 50 mg. of cortisone acetate intramuscularly six-hourly. (4) Penicillin, 500,000 units, was given twice daily.

Twelve hours after admission the pulse rate rose to 100, respirations to 10, and the B.P. to 110/70. Three hours later he regained consciousness and asked for a cup of tea. His voice was deep and his speech slow. He knew who he was and took an interest in his surroundings. Twenty-eight hours after admission he had an epileptiform fit and became comatose. Respiration ceased, and was maintained by intermittent positive-pressure inflation through a cuffed endotracheal tube via a tracheotomy. He died 78 hours after admission.

Post-mortem Findings

External appearances:—The body was that of an adolescent male with thick lips, low receding forehead, and slanting eyes; there was also a recent tracheotomy wound. In some places the tissues were gelatinous. *Central nervous system*:—The brain weighed 1,280 g.; no significant abnormality was seen. *Trachea and lungs*:—The right lung weighed 280 g. and the left 270 g.; both pleural spaces contained large quantities of straw-coloured fluid; both lungs were congested. *Cardiovascular system*:—The heart weighed 240 g.; the pericardium contained straw-coloured fluid; no significant abnormality was found. *Alimentary tract*:—The liver weighed 880 g.; no significant abnormality was found in the tract. *Urogenitals*:—The kidneys together weighed 250 g. *Reticulo-endothelial system*:—The spleen weighed 100 g. and showed no significant abnormality. *Endocrine system*:—The adrenals were normal in size and appearance; the testes were in the scrotum and showed no significant abnormality; the thyroid was small and rather firm, probably fibrous; the pituitary was not examined as the sella turcica was removed intact.

Histology.—The thyroid gland was dissected off the trachea and found to weigh 27 g. Histological examination revealed that its weight was in fact considerably less, as much of the tissue weighed was voluntary muscle. This muscle contained localized areas of pale homogenous fibres whose appearance suggested focal degeneration or necrosis. Such thyroid tissue as there was looked fairly normal, although there was definitely some increase in the interacinar fibrous tissue. There was a fibrin thrombus in one thyroid artery. In the testis there was no active spermatogenesis. The Leydig cells were very scanty indeed and did not stain characteristically. The pituitary was normal in size and histological apearance.

Case 2

A widow aged 80 was admitted to hospital on November 26, 1957, with a fractured neck of femur. Before operation her condition was good; pulse 60, B.P. 130/70, temperature 97° F. (36.1° C.). Smith-Petersen nailing was carried out under general anaesthesia. Post-operatively she became cold and cyanosed, with a systolic B.P. of 95 mm. Hg. Plasma was given intravenously. Later she lapsed into coma with a pulse rate of 50, respirations 4, and a temperature reported as subnormal.

In retrospect it was realized that this was a case of myxoedema. Further information obtained from her brother showed that for three years she had become increasingly tired, sleeping most of the day and night. Her voice was gruff.

Examination now showed her to be deeply unconscious, with a rectal temperature of 91° F. (32.8° C.). Her skin was dry and coarse, her hair and eyebrows were scanty. No other abnormality was detected. Treatment was commenced: (1) warmth by a bed cradle, the patient protected by a blanket; (2) L-thyroxine sodium, 0.05 mg. sublingually four-hourly; (3) cortisone acetate, 50 mg. intramuscularly four-hourly; (4) penicillin, 500,000 units twice daily.

The patient died within 12 hours without regaining consciousness.

Investigations.—Hb, 60%; W.B.C. 2,600/c.mm., 65% neutrophils; serum cholesterol, 280 mg./100 ml. E.C.G. low-voltage complexes in sinus rhythm at 45/minute.

Post-mortem Findings

The body was that of an obese woman aged about 80 and 5 ft. 3 in. (160 cm.) in height. Rigor mortis was present. An old, sound surgical scar was present in the right inguinal region and a fresh surgical incision over the left hip. There was bruising of the right shoulder, right cheek, and right forehead. The skull was not injured. The brain showed no significant abnormality apart from one or two minor localized subarachnoid haemorrhages. The pituitary was small but of normal appearance. The mouth, tongue, larynx, oesophagus, and trachea were healthy. The thyroid gland was small, pale, firm, and fibrous. The lungs were oedematous and there was bilateral basal bronchopneumonia. The heart was dilated. The myocardium was flabby. There was some coronary atherosclerosis but little in the aorta.

The stomach was empty. The bowel was healthy, although the proximal part of the colon was dilated. The liver showed a minor degree of passive venous congestion. The spleen was of normal size but soft. The kidneys were healthy, as was the bladder. The uterus had a fundal fibroid. The pancreas and adrenals appeared normal. The adrenal glands together weighed 13 g. Histological examination showed no significant abnormality in the adrenal glands or in the ovary, breast, and pituitary. The thyroid

gland, which weighed 17 g., was pale, firm, and fibrous. Histological examination showed it to consist almost entirely of fibrous tissue in which there were a few groups of atrophic thyroid acini, each group being infiltrated by lymphocytes. There were a number of large blood vessels in the fibrous tissue, some of which were calcified.

The appearances were those of a primary failure of the thyroid gland and suggestive of a long-standing case of Hashimoto's disease.

Case 3

A spinster aged 79 was admitted to hospital in coma on December 17, 1957. She had remained well until five months before admission, when she became slowly lethargic and intolerant of cold. On the evening of admission she was found comatose in a chair before a warm fire in a well-ventilated room.

On admission she was unconscious, with no response to noxious stimuli. Her skin was smooth and dry, and had a corpse-like coldness. Her body hair was completely absent, and had been from the age of 18. The rectal temperature was 91° F. (32.8° C.), pulse impalpable, apex rate 60, systolic B.P. 100 mm. Hg.

Investigations.—Hb, 84%; W.B.C., 10,200, normal differential count; blood cholesterol, 200 mg./100 ml.; serum sodium, 152 mEq/l.; serum potassium, 5.1 mEq/l.; plasma chlorides, 69 mEq/l.; C.S.U., a trace of protein only; liver-function tests, within normal limits; Kahn negative; blood urea, 44 mg./100 ml.; urea clearance, 60% of average normal function. E.C.G. showed low-voltage complexes in all leads.

Treatment was begun immediately: (1) Nursed between blankets, no external heat; (2) L-triiodothyronine, 0.08 mg. intravenously on admission, and 0.02 mg. sublingually four-hourly; (3) cortisone acetate, 50 mg. four-hourly intramuscularly; (4) crystalline penicillin, 500,000 units intramuscularly twice daily.

Twelve hours after admission her temperature had risen to 97° F. (36.1° C.). She spoke occasionally in a slow deep voice. A further 0.08 mg. of triiodothyronine was given intravenously. Thirty-six hours after admission her temperature was 100° F. (37.8° C.) and a few crepitations could be heard at the left base. She was then given cortisone, 50 mg. six-hourly orally. Forty-eight hours after admission she relapsed into coma once more, but recovered 12 hours after receiving a further dose of 0.08 mg. of triiodothyronine intravenously. From that time she made an uneventful recovery, at first on oral L-thyroxine sodium and later thyroid *B.P.*

Although tests on pituitary function could not be carried out owing to lack of co-operation, the fact that the patient gave a further response to intravenous triiodothyronine after lapsing into coma a second time and that she has remained greatly improved on thyroid alone for three months shows this to be a case of true myxoedema and not hypopituitarism.

Sheehan (1956) states that thyroid given alone has no beneficial effect on the symptoms of hypopituitarism.

Discussion

Hypothermic coma is the natural termination of untreated, uncomplicated myxoedema. Its occurrence has been recognized only within the last five years, although a similar picture presenting in hypopituitarism has been known for longer (Sheehan and Summers, 1952).

In addition to these three cases, 15 cases have been reported to date (Le Marquand, Hausmann, and Hemsted, 1953, 1955; Summers, 1953; Malden, 1955; Reid, 1955; Marshall and McCaughey, 1956; Dyson and Wood, 1956; Anderson and Hausmann, 1956). Of these, only one reported in the series of Malden survived. Karhausen and Zylberszac (1955) described a case without hypothermia.

The rarity of this condition is more apparent than real. Including this series, five series account for 16 patients. Once seen and recognized, the clinical picture is never forgotten. The patient is corpse-like in appearance. Occasional respirations indicate that life is still present. The usual features of myxoedema are present.

Sheehan and Summers (1952), in discussing hypopituitary hypothermic coma, state that a major factor causing the failure to recognize a hypothermic state is that the clinical thermometer records only to 95° F. (35° C.), anything lower being recorded only as subnormal. They emphasize that all patients with subnormal temperatures *must* have their temperatures measured by a low-reading thermometer. Hypothermic coma has not been reported previously in juvenile myxoedema.

Precipitating Factors.—Cold:—The reported cases show a marked seasonal incidence occurring between October and April. *Trauma:*—Case 2 went into coma following the fracture of her femur and the subsequent operative procedures. It is likely that during periods of stress the requirement of thyroid hormone increases like that of the adrenal corticosteroids.

Treatment

The condition is due directly to lack of thyroid hormone. Treatment is to give this. Although this appears simple, 15 of the 17 patients have died.

1. *Thyroid Hormone.*—3:5:3-L-triiodothyronine is the most active thyroid hormone readily available. Dyson and Wood (1956) gave a dose of 1,200 mg. followed by 1,000 mg. 36 hours later. Anderson and Hausmann (1956) described a case given 50 mg., in which anginal pain and cardiac failure developed. Both patients died. Goolden and Burrell (1957) suggest that 10 mg. 12-hourly be used initially. The third patient in this series received approximately 80 mg. of L-triiodothyronine intravenously per 24 hours. This produced a clinical response without untoward effects in a patient aged 79. It is suggested that thyroid hormone acts as a metabolic catalyst at cellular level. As such it would be less effective at low temperature. Hypothyroid patients with low temperatures probably tolerate thyroid hormone better than those at normal body temperature, the tolerance increasing with the degree of body hypothermia. If this is true, as I believe it is, then one should give an amount of triiodothyronine proportionate to the degree of hypothermia, reducing the amount as the body temperature rises to normal, then slowly increasing to the optimum dosage. A suggested scheme would be to give 100 mg. 12-hourly until the body temperature begins to rise, then reduce to 50 mg. 12-hourly or lower, depending on response of temperature and pulse rate. Maintenance dosage could then be worked up gradually when the patient is able to take the triiodothyronine orally.

2. *Rewarming.*—This can be done by immersion in warm water, by nursing between blankets, or by heat cradle. Care must be taken to avoid cutaneous vasodilatation. Rewarming is illogical and probably dangerous. Hypothermia is only a symptom of the disease state and will improve as the latter responds to treatment. Administered thyroid hormone will produce warmth that is diffuse, gradual, and physiological. No external heat was applied to the third patient in this series, who survived.

3. Intravenous fluids should be restricted on three accounts: (1) the danger of myxoedema heart failure; (2) the occurrence of acute tubular necrosis has been demonstrated secondary to hypothermic muscle damage (Marshall and McCaughey, 1956); and (3) the physiological requirement of fluid is small, as fluid loss is reduced and metabolic need low. Our successful case was given no intravenous fluid.

4. Antibiotic cover must be given.

Two further cases of severe myxoedema with marked hypothermia have come under our care. They have not been included in this series, as coma and death occurred rapidly before treatment could be initiated. In the case which came to necropsy no cause of death other than myxoedema was found. This suggests that hypothermia is an indication to start treatment immediately even when coma does not appear imminent.

Summary

Hypothermic myxoedema is an uncommon condition with a high mortality rate, recognized only in the last

five years. Three further cases are presented; one is the first reported case of coma in juvenile myxoedema, another the second case reported to have survived. This patient is still alive nine months after starting treatment.

The treatment is reviewed and discussed. It is suggested that hypothermia in itself is an indication for immediate treatment, that the application of external warmth is unwarranted, and that thyroid hormone be given in a dosage related to the degree of hypothermia.

I wish to express my appreciation of the valuable assistance given by Dr. Peter Harvey, consultant pathologist, who carried out the post-mortem examinations and microhistology. I am indebted to Dr. P. R. Duncan and Dr. I. McD. G. Stewart, consultant physicians, and to Mr. J. K. Wright, consultant orthopaedic surgeon, for permission to report the cases under their care.

Note.—Since this paper was accepted for publication a further case of myxoedema coma has been reported by S. J. Surtees and S. Ginsberg, *Postgrad. med. J.*, 1958, **36**, 443. Their patient was resuscitated but died of cardiac failure a month later.

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Medical Memorandum

Bilateral Polycystic Disease of Kidney Complicated by Intestinal Obstruction

The following case of bilateral polycystic disease of the kidney developed acute large-gut obstruction two days after admission to hospital. The case is reported because of the development of this unusual complication.

Case Report

A Sea Dyak woman aged 38 was admitted to a small out-station hospital in Sarawak, British Borneo, on July 1, 1957, 17 days after delivery of a stillborn child. She complained of cough with white sputum since delivery and frequency of micturition for two days, urine being voided a countless number of times day and night. For the 24 hours prior to admission she complained of a dull aching pain in the left lower chest, left hypochondrium, and left loin, worse on coughing, and a colicky pain in the left loin. She had haematuria for 24 hours, blood occurring throughout the stream.

On admission she was very ill and toxic, with a temperature of 103° F. (39.4° C.), and pulse 112. There was a hard fixed tender mass with an irregular surface in the left loin extending downwards below the level of the umbilicus. The right kidney was palpable, with a soft smooth mass about the size of an orange comprising the lower pole. Air entry was reduced at the left lung base, and there were fine inspiratory and expiratory rales. Blood: Hb, 45% (Sahli); red cells, 2,600,000; white cells, 8,800 (polymorphs 70%, lymphocytes 28%, eosinophils 1%, large monocytes 1%); E.S.R., 137, Westergren. Urine: acid, albumin ++, over 100 red cells per high-power field. Blood urea was 70 mg. per 100 ml.

A clinical diagnosis of bilateral polycystic kidneys with infection of the left kidney was made. Unfortunately further investigation could not be carried out in a small out-station hospital with limited laboratory and no *x*-ray facilities.

Procaine penicillin, 500,000 units twice daily, and streptomycin, 0.5 g. twice daily, brought little change in her general condition. Two days after admission she complained of generalized colicky abdominal pain. She had passed a very small stool that morning and no flatus all day.

There was moderate distension of the lower abdomen, most pronounced in the right iliac fossa, with marked visible peristalsis. An enema gave a very poor result.

Operation.—The abdomen was explored through a McBurney incision. The lower ileum, caecum, and ascending and transverse colon were greatly distended. The descending and pelvic colon were collapsed. Through the upper part of the wound the lower pole of the right kidney was seen to be covered with cysts up to 1 in. (2.5 cm.) in diameter, varying from blue to brown in colour. The whole right kidney was felt to be involved. The left kidney was greatly enlarged. Details were obliterated by pericapsular oedema. A caecostomy was performed and a Paul tube inserted.

Post-operatively the patient was put on daily washouts through the caecostomy and was given sulphaguanidine to prepare her for any further operative intervention required.

After operation the pains in her left lower chest, left hypochondrium, and left loin started to subside, and had disappeared by July 6, the third post-operative day. The left kidney was correspondingly smaller, softer, and no longer tender. From admission to operation her temperature had shown daily variations between 103 and 99° F. (39.4 and 37.2° C.). It fell rapidly after operation, and she was apyrexial on July 7. On July 8 the Paul tube fell out and she opened her bowels. She continued to have a normal daily motion until discharge from hospital.

On July 12 the caecostomy was separated from the abdominal parietes and closed. Appendicectomy was carried out to avoid future confusion. The abdomen was closed in layers.

She was discharged from hospital on August 2 feeling very well, having refused further investigation and treatment at a larger hospital. Four months after operation she remained well and symptom-free.

Comment

Cleland (1951) reported that Dr. W. A. Giles removed a polycystic kidney (side not stated) causing intestinal obstruction in 1905. No other reference to this complication was found in the literature.

The development of acute intestinal obstruction in this patient gave rise to some diagnostic confusion, occurring as it did in a small out-station hospital where diagnosis mainly rests on history and physical examination. It caused a primary inflammatory lesion of the large bowel to be considered as an alternative diagnosis. In view of the limited surgical facilities available, the formation of a caecostomy was decided upon as the simplest way of relieving the obstruction. The decision was not regretted in view of the beneficial effect it had on the course of the illness.

A possible explanation of the clinical picture described is that ulceration of the splenic flexure occurred secondary to infection of the adjacent polycystic kidney. The passage of faeces over the ulcer perpetuated the renal infection and the colon became obstructed by inflammatory oedema. The renal infection and ulceration of the colon resolved rapidly when the colon was defunctioned by caecostomy.

The case reported does not bear out the statement of Duff (1948) that infection of a polycystic kidney affects the prognosis adversely, at any rate so far as the immediate prognosis is concerned. It is possible that the prognosis in this case may be favourably affected by a diet mainly consisting of rice with little added protein.

I wish to thank the Director of Medical Services, Sarawak, for permission to publish.

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Reviews

CANCER

Cancer. Edited by Ronald W. Raven, O.B.E. (Mil.), T.D., F.R.C.S. (Vol. 1—pp. 539+19+x; Vol. 2—pp. 641+24+ix; Vol. 3—pp. 483+18+viii; illustrated. 85s. each volume.) London: Butterworth and Co. (Publishers), Ltd. 1957-8.

The publication of this systematic work on cancer was expected with interest, and the first three volumes which have now appeared are certainly satisfying. The production is all that one could wish; the volumes are of a handy size, the illustrations numerous and apposite, the contributors acknowledged experts, the articles well documented, and the editing careful and efficient. Though all three volumes are of general interest, they will each have their special appeal to different sections of the profession. The first volume will be of great interest to the research worker and biochemist. After a brief chapter on the historical aspects of cancer (by Dr. Bett) there come two articles by the late Sir Ernest Kennaway dealing with the carcinogenic properties of cholesterol and the incubation period of cancer; the latter is a hitherto rather neglected subject. Then follow a chapter on the general question of carcinogenesis and two informative articles on the biochemistry of cell division and its relation to cancer; this section will be invaluable to the research worker, but the uninitiated (such as the reviewer) will have to make their own glossary of initials —for example, D.A.B., A.A.F., D.N.A., 5H.T., and the like. The volume ends with excellent accounts of the relation of viruses, hormones, radiation, and environmental factors to the causation of cancer. A chapter on the genetic control of cancer is also included. The second volume will greatly please the clinician and the morbid anatomist, for it describes with a wealth of illustration the local features of cancer in the different parts of the body. It is a volume to be viewed rather than reviewed.

Volume 3 opens with a thought-stimulating chapter on the immunological aspects of cancer by Professor H. N. Green, who brings evidence to show that "antigenic loss is the *raison d'être* of the cancer cell." The value of comparative pathology is then stressed in a chapter by J. R. M. Innes, who writes on the malignant diseases of domestic animals. The interesting statistical survey by Percy Stocks affords little comfort to those who are fond of cigarette-smoking. There is a section of more than 100 pages on the geography of cancer; both the epidemiologist and the general reader will want to study this. Occupational cancer is nowadays attracting increasing attention, and the hundred pages devoted to this subject are noteworthy; the possible relationship between occupational exposure and leukaemia is well discussed by Ethel Browning. There is a short section on that debatable subject—cancer education. One notes that in the U.S.A. special instruction is given to nurses on the subject of cancer and that a "Cancer Source Book for Nurses" has been distributed gratis to 131,000 nurses and nursing instructors. Volume 3 ends with a short section on some simple methods of value in the diagnosis of cancer; the useful caution is given that when "cytology is used as the only diagnostic aid, false negative reports are very much more serious."

These three excellent volumes whet our appetite for those still to come.

ZACHARY COPE.

LAURENCE-MOON SYNDROME

On Hereditary Digital Anomalies. Part III: *The Laurence-Moon Syndrome.* By Julia Bell, M.A., F.R.C.P. (The Treasury of Human Inheritance, vol. 5.) (Pp. 51-96; illustrated. 20s.) London: Cambridge University Press. 1958.

This full analysis of the literature on the Laurence-Moon syndrome follows the arrangements in the other volumes in the series. The relatively short text of 14 pages is based on 189 papers; the seven plates contain 181 pedigrees, all but a few being pedigrees of families showing the syndrome. The hard core of the monograph consists of the 26 pages of summaries of the individual papers.

In presenting a critical analysis of the literature, Dr. Julia Bell stresses that adiposity and the ocular defect are the two most constant features, being present in over 90% of cases; mental defect is almost as frequent; the digital anomaly is noted in some 70% of cases, and genital hypoplasia in just over 50%. This latter she regards as an understatement—a view supported by the fact that the incidence recorded for females is considerably lower than that recorded for males. The expectation of life for patients with this syndrome appears to be rather low, whilst the incidence of stillbirths and deaths early in life is probably high. Dr. Bell holds that the syndrome may be even more extensive than is suggested by its bizarre component—malformations of the urogenital tract in particular may be common—and stresses the need for examination of stillborn sibs of affected individuals, especially as post-mortem examinations of patients with the syndrome have so far given only sparse results.

A clarification of the pathology of the syndrome would help in two other directions. On the one hand it has been questioned whether the syndrome is not itself a mixture of two distinct affections—one being the syndrome as usually understood and the other an allied condition with neurological components—the findings apparently present in the original cases recorded by Laurence and Moon and subsequently by Jonathan Hutchinson. On the other hand the status of allied syndromes, such as the cases recorded by Biemond, by Kapuscinki, by Refsum, and by others, also requires definition. It is clear that this recessive affection with its exceptionally high rate of consanguinity—somewhere between 25 and 40%—is not polygenic but pleiotropic in type, but the limits of this pleiotropism are by no means clear. Dr. Bell's review should help matters forward, but it is rather puzzling why this study should appear as part of the volume on hereditary digital anomalies.

ARNOLD SORSBY.

HYPNOTIC PAINTING IN TREATMENT

Hypnography: A Study in the Therapeutic Use of Hypnotic Painting. By Ainslie Meares, M.B., B.S., B.Agr.Sc., D.P.M. (Pp. 271+viii; illustrated. 58s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

In the 4,000 years over which the vast literature on hypnosis extends it has included contributions which have in their time materially changed the trend of psychopathological thinking. But this precious metal lies hid beneath a deep layer of dross—mystical, bombastic, repetitive, and burdened with the alchemistic speculations inevitably stimullated by an unsolved phenomenon of nature, as hypnosis still is. Any part of the annual spate of first and last editions on this subject has, therefore, to be scanned with the question well in mind, "Does it add anything to the sum?" A case can be made out for saying that Dr. Meares has made a modest addition to the technique of using hypnosis as a means of exploring the mental mechanisms which underly psychoneurotic breakdown. The author is a practising psychotherapist bent on finding shorter and more economic ways to therapeutic insight than can be attained by orthodox psycho-analysis. From his previous writings it is evident that he combines great technical experience of hypnosis with an interest in the psychodynamic and symbolic meaning of artistic expression. He claims no more than that the uninhibited symbolism of the drawings made in the hypnotic state is as much of a *via regia* to unconscious motive as is the interpretation of dreams, and that in this condition the patient's distortions and defences are less in evidence. His material, consisting of five chronic psychoneurotic patients with evident constitutional loading, is small, and the subsequent fate of these is not discussed in detail. The technique, however, including the author's methods of passive and non-authoritarian induction

of hypnosis, is most convincingly described, and the results are reproduced in terms of black-and-white paintings. Description and theory are kept apart, so that the reader need not be biased by the author's interpretations. No excessive claim is made for the method, which is presented simply as a projective medium likely to produce material which might not otherwise come to light for a long time and which serves to signpost the progress of insight therapy. The pictures are less decorative than the symbolic paintings in the author's *The Door to Serenity*, and many of them are uninhibited *graphiti* which would arrest the eye of any zealous customs official—were this not Psychiatry. The emphasis is on the revelation of traumatic experiences in the early manner of Breuer and Freud, and one is tempted to think that Melbourne is not far behind old Vienna in producing exotic material.

The book is as well produced as it should be for the price. The pictures and therapeutic dialogue make easy reading marred only, perhaps, by the quotations of set-book banality which precede each chapter.

ALEXANDER KENNEDY.

POPULAR INTERPRETATION OF MEDICINE

Medicine and Man. The Story of the Art and Science of Healing. By Ritchie Calder, C.B.E. (Pp. 256. 16s.) London: George Allen and Unwin, Ltd. 1958.

Science, growing ever more complex and more highly specialized, has become steadily less intelligible to the average man. Accordingly it is desirable, and even essential, that the message of science should be interpreted and rewritten in popular language. The interpretation of science is not an easy branch of literature, as it demands a combination of qualities possessed by only a few authors. Among them Mr. Ritchie Calder takes a high place. He has already delighted many readers with his *Profile of Science*, his *Science Makes Sense*, and other works, and now he has turned his attention to medicine, the science of humanity.

Medicine no less than science demands interpretation, and it is of great importance that the story should be presented in language as accurate as it is attractive. The present author fulfils all our needs for correct statement. In the compass of 250 pages he has packed an amazing mass of detail regarding the art and science of healing. His book contains 12 chapters, and within them no fewer than 139 smaller sections, each of which might be read in isolation, although it forms part of a coherent and fascinating narrative. Taking a wide survey of time and space, the writer scans the pages of history from the days of demons and demi-gods to those of the World Health Organization, and discusses treatment from "eye of newt and toe of frog" to folic acid and penicillin. Naturally, he employs the historical approach, the most logical basis of modern medicine, but his book does not pretend to be either a history of medicine or a work of reference. It is rather a popular account of medical science and practice as it stands to-day and of the varied sources from which modern medical knowledge has been drawn. As is shown in the early chapters, some of these sources were in unexpected quarters. The witch, the monk, the soldier, the dairymaid, and many other folk remote from medicine as we know it, each contributed a share, albeit unwittingly. The early magico-religious attitude towards sickness and disease, however irrational it may appear to us to-day, at least laid stress upon the importance of the whole man and of the interrelationship of mind and body.

The five central chapters of the book deal with "The Great Advances," and include a wealth of information, classified under interesting subheadings, such as "Brain Waves," "Alice-in-Wonderland Drugs," "Rasputin Stomach," "Emotion Buffer," and "Radio-active Mosquitoes." Medical readers will find here not only much food for thought but also assistance in the solution of that daily problem of what to tell the patient. "Victory over Pain" and "Victory over Germs" are the next subjects of discussion, the former giving a brief but informative history of anaesthesia, the latter a picture of the antibiotic weapons which have been so effective in the microscopic war of recent years. Unsolved mysteries are mentioned, as are "Jungle Moulds" (chloromycetin), "Butterfly Wings," "Smoking and Cancer," "Stroke," and "Allergies," to quote only a few more titles. The treatise ends with the definition of health as "complete physical, mental and social well-being, and not merely the absence of disease or infirmities," and with a quotation from Descartes: "If there is any possible means of increasing the common wisdom and ability of mankind, it must be sought in medicine."

This new interpretation of medicine and of its spectacular achievement deserves to be read thoughtfully by doctor and patient alike.

DOUGLAS GUTHRIE.

PUERTO RICANS IN NEW YORK

80 Puerto Rican Families in New York City. Health and Disease Studied in Context. By Beatrice Bishop Berle, M.D. (Pp. 331+xii. 38s.) New York: Columbia University Press. London: Oxford University Press. 1958.

As American citizens Puerto Ricans can move freely within the United States, and many of them go to New York for the same reasons as Jamaicans go to Birmingham—in the hope of improving their circumstances. Because in addition to their poverty they face language and other difficulties, their arrival in increasing numbers has created serious problems for the city authorities. Dr. Berle's book reports the results of a study of 80 families for whom she provided medical services. These families were living in slum property, and the greater part of the book is concerned with their social circumstances—education, religion, reasons for immigration, family organization, housing, difficulties of language and communication, and welfare. There is also a brief account of medical conditions encountered in the Puerto Ricans, with proposals for their medical care.

T. MCKEOWN.

The principal change in the twelfth edition of *Cunningham's Manual of Practical Anatomy* (London, Oxford University Press. Vol. I: Upper and Lower Limbs, pp. 394, 25s.; Vol. II: Thorax and Abdomen, pp. 492, 28s.; Vol. III: Head and Neck, Brain, pp. 520, 28s.) is the use of English equivalents of the Paris Nomenclature approved in 1955. Some of the more familiar terms of the older Birmingham Revision have, however, been retained pending adoption of the new nomenclature in its entirety. Another change, which will appeal to the student, is the use of a new waterproof binding material which will permit cleaning with soap and water after use in the dissecting-room. In this edition, which has been revised by the late Professor J. C. Brash, a number of the illustrations in use since the first edition have been replaced.

Recent Outbreaks of Infectious Diseases (408 pp.; H. K. Lewis and Co. Ltd., 1957, 35s.) is a well-documented account of epidemics of viral, rickettsial, and bacterial infections which have occurred in Britain in recent years, by S. Leff, Medical Officer of Health for Willesden. A general description of each disease, with historical background and clinical features, is included, and space is also given to an outbreak of lead poisoning in Rotherham and the "smog" incident in London in December, 1952.

Absorption Spectrophotometry, by G. F. Lothian (2nd ed., pp. 246; Hilger and Watts Ltd., 52s.), is a concise account of the principles, practical applications, and techniques of absorption spectrophotometry. In this edition more detailed attention is devoted to photoelectric instruments, which have largely displaced photographic and visual methods. An extensive bibliography is included.

The second edition of *Systemic Ophthalmology*, edited by Professor Arnold Sorsby (pp. 701+xiv; Butterworth and Co., Ltd., £5 5s.), has been revised throughout; some new chapters have been added dealing with subjects in which particularly rapid advances have been made. The book, which is of composite authorship, deals with the many conditions in which ocular disease is related to systemic disorders. It is fully illustrated, the coloured plates being especially well reproduced.

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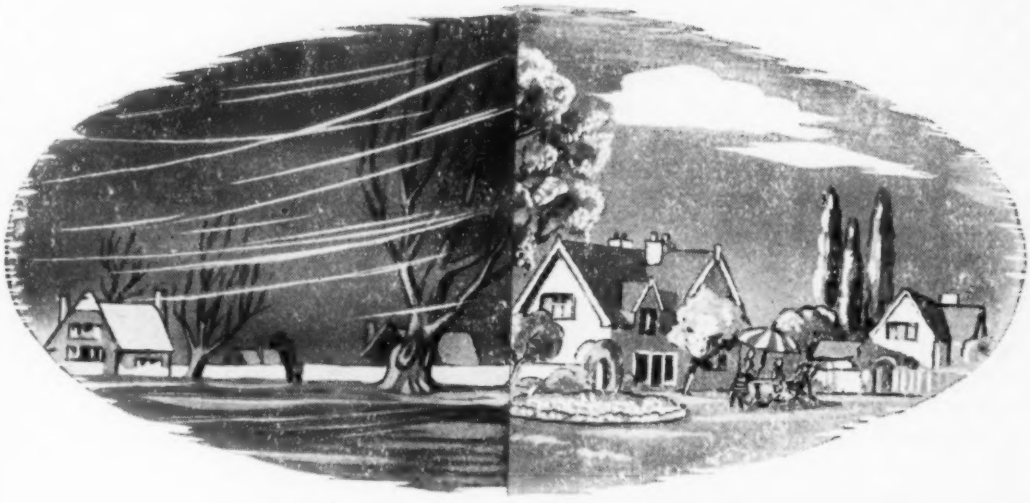

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DRUGS AND LIVER DISEASE

Drugs may adversely affect the liver in several ways—for instance, by causing hepatic necrosis, intrahepatic biliary obstruction, or fatty change in the hepatic cells. In addition the syndrome of hepatic precoma and coma may be caused or aggravated by drugs given to a patient with pre-existing liver disease.

Acute hepatic necrosis, characterized clinically by jaundice, hepatomegaly, and in severe cases hepatic coma, haemorrhagic manifestations, and rapidly deepening jaundice, may be caused by a variety of toxic agents. The chlorinated hydrocarbons such as carbon tetrachloride, benzene, and quinoline derivatives, muscarine, and various metallic compounds are examples of such agents. Drugs used in the treatment of epilepsy—namely, phenytoin sodium[1] and phenacemide (" phenurone ")[2]—have been similarly implicated, and recent reports[3 4] show that the use of a derivative of isoniazid, iproniazid (" marsilid "), will cause both abnormal liver function tests and jaundice associated with hepatic necrosis in some patients treated with it.[5] Originally introduced as an antituberculous agent it has more recently been claimed to be of use in the treatment of myocardial ischaemia and as a " psychic energizer." Fatalities from hepatic necrosis have followed its use and that of another nicotinic acid derivative pyrazinamide,[6] which also limits this drug's value as an antituberculous agent.

The list of drugs causing jaundice by another mechanism—namely, intrahepatic biliary obstruction—is an ever-lengthening one. At present owing to its common usage chlorpromazine (" largactil ") is the most important, for jaundice occurs in 1–2% of cases treated, but other drugs, including arsphenamine, dinitrophenol, methyltestosterone, norethandrolone (" nilevar "), thiouracil, *p*-aminosalicylic acid (P.A.S.), sulphadiazine, and methimazole, may also produce this syndrome. Clinically, after a latent period of up to three weeks, an obstructive type of jaundice with pruritus, pale stools, and dark urine begins. Usually this condition is clinically mild, but severe cases have been reported following arsphenamine and chlorpromazine. Jaundice of seventeen months' duration with skin xanthomata and gross increase of the serum cholesterol has followed arsphenamine. A similar case of 13 months' duration has followed chlorpromazine.[7] In a recent communication to the Section of Gastroenterology at the British Medical Association's Annual Meeting, Drs. A. E. Read and Sheila Sherlock reported one case where the jaundice following chlorpromazine had lasted over two years. Cases of jaundice and hepatic dysfunction due to promazine have been described indicating that this drug is not without some risk in this respect.[8 9] Allied to this problem is that of the treatment of the pruritus associated with jaundice caused by drugs. At least two preparations—namely, norethandrolone and methyltestosterone, which are effective in the treatment of pruritus—also can produce intrahepatic obstructive jaundice.

Fatty change in the liver has recently been produced experimentally in baboons by J. Gillman and C. Gilbert by altering the hormonal balance between insulin, thyroxine, and adrenal corticosteroids.[10] It is possible that to the list of toxic properties of steroid drugs must be added that of fatty change in the liver, a point of clinical importance in view of their widespread use.

The syndrome of hepatic precoma and coma is thought to be due to the entry of nitrogenous products absorbed from the bowel into the systemic circulation via abnormal collateral channels bypassing a damaged liver.[11] The level of ammonia in the systemic circulation has been widely used as a measure of these toxic products.[12 13] Certain diuretic drugs have been shown to bring about clinical and neuropsychiatric deterioration when given to patients with chronic liver damage and fluid retention. Ammonium chloride administered to potentiate the action of mercurial diuretics is toxic, presumably owing directly to its content of ammonia. Acetazolamide (" diamox ") can also cause neuropsychiatric deterioration,[14] and this has been correlated with failure of peripheral tissues to remove ammonia adequately from the systemic circulation.[15] Chlorothiazide is similarly toxic to patients with chronic disease of the liver, particularly if a good diuretic

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[15] Dawson, A. M., De Groote, J., Rosenthal, W. A., and Sherlock, S., *Clin. Sci.*, 1957, **16**, 413.
[16] Read, A. E., Haslam, R. M., Laidlaw, J., and Sherlock, S., *Brit. med. J.*, 1958, **1**, 963.

response is obtained by its use.[16] As the action of chlorothiazide is in part similar to that of acetazolamide, it would seem reasonable to assume that toxic manifestations appear because of interference at a peripheral site with metabolism of the ammonium ion. Other factors, however, including loss of potassium, may be of importance. It is worth keeping a watch for signs of liver damage when patients receive drugs that have been recently introduced.

OPEN DOORS

There has been a great liberalizing move in British mental hospitals in the past ten years. Many ward doors have been permanently unlocked, leave privileges increased, easier discharges allowed, and great efforts made to provide occupational therapy and work for all. The strait-jacket and the padded room have fallen into disfavour. As each old hospital is converted to the new methods, the same improvements are noted: less restraint, with more consideration of patients as individuals, is followed by fewer escapes, fewer fights, less incontinence, and a smaller bill for barbiturates and other sedatives.[1] Now these methods are beginning to spread on the other side of the Atlantic. The Milbank Memorial Fund of New York last year organized a conference[2] at which D. Macmillan described the work of Mapperley Hospital, Nottingham, and emphasized how it is possible to run a mental hospital without a single locked door, and virtually without the use of certification. This year the president's address[3] at the meeting of the American Psychiatric Association at San Francisco called for the abolition of the enormous old-fashioned state mental hospitals—some have 10,000 beds—and a fresh start along the lines already becoming familiar in Britain.

This is not the first decade in which the gospel of "no restraint" and of "occupation" has been preached[4]; indeed, the story of the mental hospital seems to show a perpetual swing back and forth between periods of harsh restriction and therapeutic freedom.[5] If the present open-door policy is to be a permanent step forward and not just another pause of the pendulum it will have to be proved to do therapeutic good, so that faith may come to be supported by works, and it will have to overcome a difficulty of communication. At present it is not always appreciated that "the unlocked door is just a symbol and should not be made a fetish."[6] Some hospitals are not applying the full prescription: either they do not know it, or they have not full confidence in it. It is not sufficient to unlock the majority of doors and provide more occupational therapy. The essential is a change of outlook in the staff, particularly the nurses, who are sometimes inclined to view the patients simply as naughty children. The open-door programme is a way of inducing them to try understanding instead of punishing, because it makes their work easier, more interesting, and possibly more fruitful. Macmillan himself believes that so long as there remains one locked ward in a hospital the nurse can still threaten the patient with imprisonment, the easy but incomplete solution,[7] and that it is only when all doors are open that the new relationship between staff and patients can begin.

Another important part of the policy is the emphasis on individuality. Every patient must have clothes which are his own, a bed, a locker, a chair, which are recognizably his and respected as such by the staff, and a social role, such as a particular ward duty, which is recognized as his too.[8] The job of all the staff, ward orderlies, porters, gardeners, as well as nurses and occupational therapists, is to make friends with individual patients, and so influence them and help to understand them. This is the way that a mental hospital changes from an institution into a therapeutic community. But this is still only half the prescription. The other half is in the hospital's external relations. By domiciliary visits, out-patient clinics, and close contact with general practitioners and with the local health authority, the physicians and social workers of the hospital will often be working with the patient and his relatives even before he first comes into hospital, and should continue an affectionate concern for both patient and family after discharge. Long and careful follow-up care is the corollary of early discharge. This may help the patient to avoid further serious breakdown, but it also serves to educate and reassure the public—and this is the crux of the matter. People are sent into a mental hospital only when they can no longer be tolerated by people outside, and they can be discharged again as soon as their behaviour returns within the tolerable limits. Different societies have different tolerances, and what they will stand can be altered by education, and by new modes of treatment or care which serve as guarantees of their security. The patient for early discharge need not be free of psychotic symptoms and

[1] Mandelbrote, B., *Ment. Hyg. (N.Y.)*, 1958, **42**, 3.
[2] Milbank Memorial Fund, *An Approach to the Prevention of Disability from Chronic Psychoses*, 1958, New York.
[3] *New York Times*, May 13, 1958.
[4] Walk, A., *J. ment. Sci.*, 1954, **100**, 807.
[5] O'Donoghue, E. G., *The Story of Bethlem Hospital from its Foundation in 1247*, 1914, London.
[6] Hunt, R. C., in *An Approach to the Prevention of Disability from Chronic Psychoses*, 1958, New York, p. 20.
[7] Macmillan, D., ibid., p. 44.
[8] Freeman, T., Cameron, J. L., and McGhie, A., *Chronic Schizophrenia*, 1958, London.

signs: it is sufficient that his behaviour conform to society's minimum demand. It is not whether he hears voices which is the test, but what he does about them. The success of the open-door policy, therefore, in the long run depends on public tolerance.

TRANSFUSION TREATMENT OF RADIATION DISEASE

During the last decade much experimental work has been done on the treatment and prevention of radiation disease. Protection by chemical means[1 2] has to be given before exposure in order to be effective, and consequently is of no help in treating either radiation casualties or radiotherapy patients who show an unwanted reaction. The most promising experimental treatment in animals is the injection after exposure of spleen homogenates or bone marrow. The injected cells colonize the irradiated animal and supply it with blood for at least some weeks after exposure. Owing to the temporary destruction of the immune response by irradiation of the whole body, the animals accept grafts from genetically different strains and even from other species. Possible human applications of this treatment have awakened interest, particularly in relation to the treatment of leukaemia, aplastic anaemia, and the possible grafting of a kidney in some forms of uraemia.[3]

Haemorrhage, thrombocytopenia, anaemia, and agranulocytosis are prominent among the killing effects of acute radiation, and naturally various forms of blood transfusions have been used experimentally in animals to combat their effects. American work has shown that in dogs normal whole blood was of little value[4 5] unless a massive cross-transfusion was undertaken.[6] Transfusions of leucocyte concentrates in dogs were considered promising, as the transfused leucocytes were found to migrate to sites of infection.[7 8] Concentrates of platelets when transfused into irradiated dogs and rats were found to correct defects in haemostasis.[11 12] This response is of interest because dogs resemble man in being very prone to post-irradiation haemorrhage. A rather different type of transfusion treatment was found to be successful in mice.[11 12] A particular type of transplantable carcinoma induces a leukaemoid reaction, and blood taken from mice bearing this tumour was given to irradiated (non-tumour-bearing) mice of the same strain: a single injection was found to give protection. The leukaemoid blood contained very large numbers of mature and much smaller numbers of immature granulocytes, but the single injection contained too few granulocytes to combat infection. The most likely explanation of the beneficial effect was that the leukaemoid blood acted in a similar way to marrow injections and repopulated the damaged haemopoietic tissue by means of the immature cells it contained.[12]

Professor Bagdasarov has recently described Russian experience with transfusion therapy in radiation disease.[13] Platelet concentrates and leucocyte concentrates with some platelet contamination reduced the death rate in dogs subjected to high doses of *x* rays and also greatly improved their haematological response. Leucocyte concentrates, again with platelet contamination, were also given to patients with low white-cell counts after radiotherapy. Good results were claimed in 80% of 250 cases, but only 3 were described. In the most striking, a post-irradiation white count was raised from 2,600 per c.mm. to 4,900 per c.mm. by means of five transfusions, even though a second course of radiotherapy was given at the same time.

Transfusion treatment probably acts merely as replacement therapy, but, given the correct conditions, the leucocyte concentrates may possibly act in a similar way to bone-marrow grafts and leukaemoid blood transfusions. Recently experiments have been reported[14] in which normal human blood was incubated *in vitro* with tritium-labelled thymidine, a radioactive precursor of D.N.A. Labelling was seen in a small percentage of large mononuclear cells, which were identified as monocytes or large- and medium-sized lymphocytes. This strongly suggests that in normal blood a few leucocytes are actively synthesizing D.N.A. preparatory to mitosis, and the authors were inclined to regard them as totipotential haemopoietic cells in transit. If this conclusion is correct, leucocyte concentrates could colonize damaged haemopoietic tissue if a large enough dose of whole-body irradiation was given to overcome the immune response. This may have occurred in the case of the heavily irradiated dogs,[7 8 13] but is most unlikely to have taken place in the patients given radiotherapy,[13] who, having received irradiation to only part of the body, would retain an intact immune reaction.

[1] Patt, H. M., *Physiol. Rev.*, 1953, **33**, 35.
[2] Bond, V. P., and Cronkite, E. P., *Ann. Rev. Physiol.*, 1957, **19**, 299.
[3] *Blood*, 1958, **13**, 266.
[4] Allen, J. G., Basinger, C. E., Landy, J. J., Sanderson, M. H., and Enerson, D. M., *Science*, 1952, **115**, 523.
[5] Furth, F. W., Coulter, M. P., Miller, R. W., Howland, J. W., and Swisher, S. N., *J. Lab. clin. Med.*, 1953, **41**, 918.
[6] Salisbury, P. F., Rekers, P. E., Miller, J. H., and Marti, N. F., *Science*, 1951, **113**, 6.
[7] Brecher, G., Wilbur, K. M., and Cronkite, E. P., *Proc. Soc. exp. Biol. (N.Y.)*, 1953, **84**, 54.
[8] Cronkite, E. P., and Brecher, G., *Ann. N.Y. Acad. Sci.*, 1955, **59**, 815.
[9] —— Jacobs, G. J., Brecher, G., and Dillard, G., *Amer. J. Roentgenol.*, 1952, **67**, 796.
[10] Woods, M. C., Gamble, F. N., Furth, J., and Bigelow, R. R., *Blood*, 1953, **8**, 545.
[11] Congdon, C. C., McKinley, T. W., Sutton, H., and Urso, P., *Radiat. Res.*, 1956, **4**, 424.
[12] Smith, L. H., and Congdon, C. C., *Arch. Path. Lab. Med.*, 1957, **63**, 502.
[13] Bagdasarov, A. A., *et al.*, *Second United Nations International Conference on the Peaceful Uses of Atomic Energy*, 1958. A/CONF.15/P/2238.
[14] Bond, V. P., Cronkite, E. P., Fliedner, T. M., and Schork, P., *Science*, 1958, **128**, 202.

SERUM TRANSAMINASE IN MYOCARDIAL INFARCTION

The important features of serum glutamic oxaloacetic transaminase (S.G.O.T.) in clinical medicine have already been noted in these columns.[1 2] It is an enzyme which is concerned in the reversible transfer of amino groups, and is therefore present in many tissues, particularly the heart, liver, brain, and kidneys. Damage to these and other tissues results in the liberation of the enzyme into the serum, where it can be estimated by relatively simple biochemical techniques.[3 4] Care should be taken to avoid haemolysis when obtaining a sample of blood. Interest has centred round the value of S.G.O.T. as a test for myocardial infarction, and there is now enough evidence on which to base an estimate of its place in diagnosis. When an infarct has occurred the level of S.G.O.T. rises quickly during the first day or two and then quickly falls to normal again by about the fifth day. The peak concentration, which may be ten or twenty times the normal level (5–40 units per ml.), is usually reached between 36 and 72 hours after the onset. False negatives—that is, no rise in the presence of a confirmed infarct—are said to occur in 5–10% of cases, but some of these may be due to failure to detect a very transient increase in S.G.O.T. High values, on the other hand, are found in association with liver disease, acute pancreatitis, cerebrovascular accidents, and myocarditis, and after operations, severe trauma, or haemolysis. Neither pericarditis nor pulmonary infarction causes any alteration in S.G.O.T.

The authors of the two papers we publish this week have attempted not only to assess the usefulness of the test but also to define its relation to some of the finer points of diagnosis and prognosis in myocardial infarction. Dr. H. A. Dewar and his colleagues, for example, have found that the rise in S.G.O.T. appears twenty-four hours earlier than fever or a rise in the sedimentation rate. It is a "more prompt, more striking, more brief, more sensitive, and more specific" indication of infarction than either of these signs. Perhaps its greatest value is in patients in whom the electrocardiographic evidence is equivocal because of previous ischaemic episodes or the presence of arrhythmias, bundle-branch block, or the effects of digitalis. Another use is in distinguishing infarction from so-called "acute coronary insufficiency," especially in those already under treatment or with minimal electrocardiographic changes. It may, however, be difficult to decide what to regard as an abnormal level of S.G.O.T. in these patients if single estimations only are done, since it is clear that values within the normal range may not be normal for a particular individual.[5] For this and other reasons Dr. R. Bruce and his colleagues recommend daily estimations during the first week, not only to follow the course of the acute episode but also to establish a baseline for the individual. They have also tried to base a prognosis on the peak concentration of S.G.O.T. found in their patients. Thus the average figure in 16 patients who recovered was 111 units, contrasting with a figure of 576 units in the seven who died. Once again such figures may be misleading when applied to the individual patient, for while experimental and clinical data suggest that there is a good correlation between the extent of the infarct and the height of S.G.O.T., many other factors are concerned in the outcome of the illness. Moreover, as Dewar and his colleagues point out, some of the highest titres are found in patients who develop acute heart failure associated with pulmonary oedema or hepatic centrilobular necrosis. Further work on the relation of S.G.O.T. to other factors which affect prognosis may prove rewarding, since the value of the test in the diagnosis of myocardial infarction appears to be firmly established.

[1] *Brit. med. J.*, 1957, **1**, 573.
[2] Ibid., 1958, **1**, 568.
[3] Reitman, S., and Frankel, S., *Amer. J. clin. Path.*, 1957, **28**, 56.
[4] King, J., *J. med. Lab. Technol.*, 1958, **15**, 17.
[5] Goble, A. J., and O'Brien, E. N., *Lancet*, 1958, **2**, 873.

HEALTH IN INDUSTRY

The publication of the first separate annual report[1] on industrial health by the Chief Inspector of Factories marks a departure from the long-established practice of presenting all aspects of the work of the factory inspectorate in a single volume. From now onwards these separate annual reports will be the chief source of information in the field of industrial health. While to a great extent this field is within the special sphere of the medical branch of the factory inspectorate, it is also the concern of the general inspectorate and of the other specialist branches, engineering and chemicals. The present report reviews the year's activities, including new legislation, industrial health surveys, advisory panels and committees of inquiry into various subjects, and accounts of certain industrial diseases and accidents. The subject of industrial dermatitis has been selected for a special chapter on its own. The report mentions that the Factories (Ionizing Radiations) Special Regulations, dealing with the use of "sealed sources," are still in draft, having been submitted for comment to representatives of the organizations mainly concerned and to other interested persons. Consideration is now being given to the preparation of regulations for the use of unsealed sources generally. Industrial health surveys were carried out in Halifax[2] and in the Potteries with a view to obtaining information about environmental conditions, existing medical and nursing services, and the adequacy or otherwise of precautions against general and specific hazards to health. An inquiry into the provisions made for giving first aid revealed some inadequacies, and discussions followed between representatives of various governmental departments and the societies responsible for the recruitment and training of first-aid workers.

Among the industrial diseases on which the report comments, lead poisoning showed a slightly increased incidence, but there were no fatal cases. A relatively new working process, entailing the use of isocyanates, caused an outbreak of acute illness, with asthma as its

[1] *Annual Report of the Chief Inspector of Factories on Industrial Health for the Year 1957*. 1958. H.M.S.O., London. Price 3s. net.
[2] See *Brit. med. J.*, 1958, **1**, 764.

outstanding symptom. Industrial dermatitis is still considered one of the principal causes of disability and lost time in industry. Figures recorded by the Ministry of Pensions and National Insurance for 1955–6 showed that the average duration of incapacity was 38 days for males and 51 days for females: the total time lost amounted to 0.86m. days, compared with 0.93m. days for 1954–5. Voluntary notifications to the factory department of the Ministry of Labour and National Service also suggested that the steady decline which has taken place during recent years was continuing. Among the many causes of industrial dermatitis mineral oil holds a prominent place; though this form of dermatitis is not often responsible for absence from work, it carries the risk of epitheliomatous ulceration. The problem presented by skin sensitization is a particularly difficult one, since repeated exposure to skin irritants may result in severe and lasting dermatitis. Once again the importance of thorough cleansing as a preventive measure is emphasized; it is even more important than the use of barrier creams. Separate reviews on selected subjects are to appear in future annual reports, and if they maintain the same high standard as the review on industrial dermatitis in this year's report they should make a valuable contribution to the study of industrial health.

LIVE INFLUENZA VACCINES

In an emergency due to the appearance of a novel and dangerous strain of influenza it would be impossible to manufacture enough conventional vaccine for millions of people in a short time.[1] There simply could not be provided, quickly, enough fertile eggs or egg incubators. In theory an attenuated living virus might be given intranasally in a dilute form and prove far more practicable in that a small number of eggs might provide enormous numbers of vaccine doses. Early attempts to achieve this end were not very promising. Viruses tested either were not sufficiently attenuated or did not produce satisfactory rises in antibody. Workers in the U.S.S.R. have for several years been testing live influenza vaccines, and promising experiments on these lines with the Asian virus grown in tissue culture were lately reported by V. M. Zhdanov[2] and his colleagues. Small-scale trials in Great Britain have been reported by A. Isaacs and his colleagues,[3 4] but the results were not very encouraging. However, the matter is being further pursued in this country and there is good contact with Russian workers. Several important questions have to be answered: Will a live vaccine give substantial immunity with a negligible number of untoward reactions? Is there danger of reversion of the attenuated virus to virulence? Can the vaccine be made on a large scale cheaply and rapidly, without the need for a fantastic number of eggs? It can readily be seen that these important questions are not likely to receive quick answers.

[1] *Brit. med. J.*, 1958, **1**, 447
[2] Zhdanov, V. M., Ritova, V. V., Orlova, A. V., Sokolova, N. N., and Golygina, L. A., *Lancet*, 1957, **2**, 735.
[3] Isaacs, A., and Roden, A. T., ibid., 1956, **2**, 697.
[4] —— Negroni, G., and Tyrrell, D. A. J., ibid., 1957, **2**, 886.

COST OF HOSPITAL DEPARTMENTS

Formidable as they are, the hospital costing returns[1] published last week deserve some study, for they claim to be the answer to the criticisms of the old costing returns, which they replaced for some hospitals on April 1, 1957. The old returns raised all sorts of pertinent questions about the comparative costs of apparently comparable hospitals without, however, providing the answers. It was therefore hoped that by means of the new returns, under which the costs would be analysed by departments—wards, works and maintenance, medical service departments, administration, laundry, and so on, each with its own share of a hospital's staff bill—an explanation would be forthcoming of why the cost of maintaining a patient in, say, the London Hospital was nearly £6 a week less than in St. Thomas's (according to the costing returns for 1956–7). In particular, since out-patient expenditure was henceforward to be separately costed, it was hoped that a truer picture of in-patient costs would be obtained than by the old returns, under which out-patient costs were eliminated by assuming that five out-patient attendances represented one in-patient day. In the event, the new returns, which cover some 200 hospitals spending more than £150,000 a year each, show that for the teaching hospitals, both in London and in the provinces, the formula was not far out, although it rather underestimated out-patient costs. In the acute non-teaching hospitals the formula underestimated them even more and should have been more like four to one. But the most interesting point that emerges from the analysis of out-patient costs is the big difference between the cost of a new out-patient in the London teaching hospitals and in other hospitals. The average cost in acute non-teaching hospitals in England and Wales for each out-patient attendance is 17s. 2d.; in provincial teaching hospitals it is 18s. 4d.; and in London teaching hospitals, £1 1s. 9d. The average cost of a new out-patient, on the other hand, in the three groups respectively is £2 12s. 10d., £2 16s. 6d., and £4 5s. 9d. The explanation is not apparently that more elaborate diagnostic techniques are used in the London teaching hospitals than elsewhere, because the analysis of out-patient costs does not include their share of the cost of the *x*-ray department or pathological laboratory, or indeed any of the medical-service departments—which must surely detract from its usefulness. In fact, the only explanation that can be gathered from these returns is that the proportion of new out-patients to total out-patient attendances is lower in the London teaching hospitals.

Thus tantalizing queries are provoked by the new returns as much as by the old. What the new returns do is to throw the questions a stage farther back. That is, if one hospital's in-patient costs are shown to be noticeably higher than in another similar hospital, one can see from these returns whether it spends more than the average in the wards, or on administration, or on works and maintenance, and so on. St. George's Hospital, for instance, which has the highest in-patient cost

[1] *Hospital Costing Returns—Year Ended 31st March, 1958.* Volume I—"Hospitals which Operated the Main Scheme," 1958, H.M.S.O., London. Price £1 12s. 6d. net.

of the undergraduate teaching hospitals (£39 2s. 9d. a week, compared with the London's £28 18s. 8d. and an average for the acute London teaching hospitals of £33 11s. 3d.), has a direct expenditure in the wards of about £1 2s. a week more than the average; it also has a heavy bill for works and maintenance and an occupancy rate for its staffed beds that is lower than the average. But the returns do not, of course, give the reasons for these differences. The unit costs of one hospital's diagnostic *x*-ray department may be twice as high as another's, so may be those of its boiler-house. But is this the result of inefficient equipment or inefficient management? Does a higher cost for the physiotherapy department represent better service, a swifter rehabilitation of patients, or sheer extravagance? It is to be hoped that the returns will provoke this sort of question among hospital authorities, and that they will insist on getting the answers; otherwise the cost of costing will merely be one more item in the heavy bill that the nation has to pay for maintaining its hospitals.

DISORDERED SOCIETY

The Home Secretary told the House of Commons last week that Britain had half as much crime again as before the war. The increase in indictable offences which began in 1955 was still rising steeply during the early part of 1958. A disturbingly high number of crimes were committed by youths between 16 and 21 years of age, and there had been a recent increase of offences committed by children under 17. Mentioning the grave lack of knowledge which hampered the work of the police and the courts, Mr. Butler said that the new research unit in the Home Office was now well established, and in due course the Institute of Criminology at Cambridge would be getting under way. In the light of Mr. Butler's remarks about lack of knowledge the recently issued annual report of the Institute for the Scientific Treatment of Delinquency is of particular interest, for the first of the objects of the Institute is "to initiate and promote scientific research into the causes and prevention of crime." If, as may be assumed from Mr. Butler's speech, other methods are failing to stop the rise in the number of young criminals, then the scientific study of the causes of crime and of the treatment of offenders should be much more actively encouraged. As the report of the Institute for the Scientific Treatment of Delinquency states: "There is more need now for the I.S.T.D. than at any other time in its existence."

The clinical work of the I.S.T.D. was taken over by the National Health Service in 1948, and its main activities are now research, education, and the publication of the *British Journal of Delinquency*. Research, which is under the directorship of Dr. H. Mannheim, is hampered by lack of funds, and education is "the one direction in which it is possible to make headway without risk of financial loss." The educational activities of the I.S.T.D. have two clear aims: "First, to support the authority of social and psychological science to establish as it were an enclave within the field of penal method. The second is to show that this can be done only by close study of the actual case-material, by proving in fact that crime is a form of behaviour disorder to be correlated with other social and psychological disorders and treated along similar lines." It is logical therefore for the Institute to press for the establishment of "observation centres" where selected offenders could be diagnosed and treated. By encouraging research on these and other lines the Home Secretary might not in the future have to give such a depressing account of what he called "a deep disorder in society."

NOBEL PRIZE IN MEDICINE

The three American geneticists who share the Nobel Prize in Medicine and Physiology have done their experimental work with organisms which are almost as different from man as living organisms could be. Yet so similar is all life at the cellular level, whether plant or animal, that these workers' researches with fungi and bacteria have contributed greatly to the development of theoretical genetics, and from them a fuller understanding of human genetics may be expected to spring. Professor G. W. Beadle, of the California Institute of Technology, and Dr. E. Tatum, of the Rockefeller Institute in New York, have shown that in the common fungal mould of bread and other substances, *Neurospora crassa*, distinct genetic changes are constantly associated with specific biochemical changes. They are thus getting at the precise mechanism by which the chromosomes in each cell nucleus transmit inherited characters. The advantage of using the somewhat recondite organism *Neurospora* is that the segregation of its genes in sexual reproduction is matched by a spatial separation of the resulting spores. By micromanipulation the spores bearing assorted genes can be plated out separately for growth on the same or different media. Thus the effect of chemical variations in the media can be studied against genetic variations in the spores, and it was found that a single genetic change resulted in a single change in dietary requirements. Professor Beadle, who is at present Eastman Visiting Professor at Oxford, is aged 55, and Dr. Tatum is 48. They share half the Nobel prize.

The other half of the prize goes to Professor J. Lederburg, aged 33, of the University of Wisconsin. With Tatum, Lederburg studied bacteria (chiefly *Escherichia coli*) with genetically altered dietary requirements, and was able to show that at least some of them undergo sexual reproduction. Later he showed, in collaboration with his wife, that bacteria could incorporate in themselves genetic material obtained from bacteriophage, and transmit it to other strains. Instead of more or less homogeneous vegetative cells dividing by simple fission, bacteria are found to be complex organisms showing segregation and recombination of genetic material in reproduction. Lederburg's work is a major contribution to the foundation of bacterial genetics, now a rapidly growing and elaborate branch of science.

Drug Treatment of Disease

DRUGS IN TREATMENT OF EPILEPSY

BY

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This paper is concerned solely with the medical treatment of epilepsy. To conform with the intention of this series of articles the word "medical" is used in its narrowest sense—pharmacological—and "epilepsy" in its widest—to include recurring discrete disorder of sensation, behaviour, or consciousness of any sort due to cerebral disturbances, whatever the prime cause. The treatment is of fits of all kinds, whether symptomatic of brain disease (for example, trauma), of disease elsewhere (for example, vascular disease), or of unknown origin (idiopathic). It would be wise to consider this against the wider, and perhaps more important, aspects of epilepsy which were presented as a symposium in this *Journal* on March 22, 1958.

Kinds of Epilepsy

For pharmacological as well as other reasons the precise form of epilepsy must be recognized on clinical grounds and, if in doubt, with the help of the electroencephalogram, because, for instance, drugs which may benefit one form of petit mal due to local brain damage may aggravate the other form with the characteristic spike-and-wave discharge in the electroencephalogram. For our present purpose epilepsy is divided into:

The general epilepsies:
  Grand mal.
  Petit mal.
Focal epilepsies.

Grand mal is a pure tonic–clonic fit, which is the same whatever the cause. Petit mal includes the brief, frequent, stereotyped "absences" of childhood and myoclonic jerking. And the focal epilepsies include all other attacks however diverse or elaborate. Treatment of grand mal and focal attacks is so similar that they will be considered together, and the word anticonvulsant will be used generically whether or not an actual convulsion occurs in the attack.

Even after full investigation and medical or surgical treatment of the cause of the fits, medical treatment of the fits themselves is subservient to management of the patient's attitude, his life, and its background. Indeed, continuation of medical treatment may become inevitable because continuing stress in the life perpetuates epilepsy in a predisposed person.

Types of Drug

The most successful anticonvulsants for practical use in the ambulant patient can be listed thus:

(*a*) Barbiturates, especially phenobarbitone and methylphenobarbitone.

(*b*) Hydantoins—phenytoin ("epanutin") and methoin ("mesontoin").

(*c*) Primidone ("mysoline").

(*d*) Diones—troxidone ("tridione") and paramethadione ("paradione").

(*e*) Others, especially acetazolamide ("diamox"), phensuximide ("milontin"), and phenacemide ("phenurone").

Though they derive from different chemical sources it is remarkable how closely similar the basic molecular formula of each group of the better anticonvulsants is.

Time of Administration

The average time of effective concentration after ingestion of an anticonvulsant is from six to eight hours, but the time of administration must be judged by the time of occurrence of fits. Some people always have them by day, some always by night, and the peak period is within an hour or so of rising. Therefore, the day's dose may be given on retiring, on rising, or spaced through the day. When fits are more frequent at the menstrual period a much larger dose may be given in that week.

Barbiturates

Occasionally, bromides have been given as a last desperate attempt to stop fits when all else had failed. But they are mentioned first to dismiss them with the comment that, though they stopped many fits, they did the epileptic person much harm in turning him into a handicapped, retarded dullard with bromism.

The first drug of choice remains phenobarbitone. This shares with aspirin and alcohol the stigma of abuse, but it remains an excellent anticonvulsant. It is safe, of very low toxicity, with little tendency to sensitivity. Do not, however, discount as neurotic the occasional patient who complains bitterly of sleepiness on a tiny dose, for some cannot tolerate it and many become depressed with it, though most become used to it after a few weeks.

It is always wise to begin treatment with phenobarbitone, ½ gr. (32 mg.) once or twice in the day, but not to use much more than this in the first instance. Children, who will require a smaller dose according to their size, may be very tolerant of it, but sometimes become irritable and difficult while taking it. If so, stop it, for they will not mend. If fits continue in spite of a reasonably small dose of phenobarbitone, do not push it, for the patient will probably become retarded or depressed, and his distress and difficulty in continuing his pattern of life will bring more fits. Instead, go on to the hydantoins.

Phemitone ("prominal"), which is methylphenobarbitone, is converted to phenobarbitone in the stomach. Its anticonvulsant dose is double that of phenobarbitone, and though its pharmacological effect should be the same, patients who are sleepy with phenobarbitone may be content with phemitone (1–3 gr. (65–200 mg.) in a dose). It is worth trying. Long-acting phenobarbitone in an "enseal" is also advised for the same purpose.

Initial sensitivity to phenobarbitone or phemitone is unusual, but the physician is occasionally surprised to see a rash which, developing years after beginning treatment, disappears on withdrawing the barbiturate.

The effects of overdosage are subtle and serious, for the sensitive patient becomes intellectually retarded, slothful, sleepy, and sometimes very depressed. These symptoms are serious because they are insidious, not recognized for what they are, and greatly handicap the epileptic in pursuing his way in life. They should be avoided, even at the cost of an occasional fit; their continuation may lead to a vicious spiral downward, with a return of fits. Never, therefore, push barbiturates or have recourse to the amphetamines to try to offset these effects. Instead, limit the dose of phenobarbitone to the patient's toleration, and add another non-sedative anticonvulsant, of which the hydantoins are the best.

Hydantoins

When phenobarbitone has been given to an adult up to a total of three ½-gr. (32-mg.) doses in the day and further treatment is needed, add phenytoin sodium (diphenyl hydantoin sodium, epanutin) 0.1 g. twice or three times a day. It may be given in a larger dose at morning or evening if fits are diurnal or nocturnal only. It is a wise generalization that the margin between the effective anticonvulsant and toxic amount is small, so that the hydantoins must be given in fairly large doses, 0.3 g. daily being usual. Most adults will develop toxic effects if they take 0.4 g. daily for a few weeks, for the substance slowly accumulates, and it may be necessary to give 0.3 g. and 0.4 g. on alternate days to control fits without toxicity.

Sensitivity results in a rash with pyrexia and transient adenitis just like German measles or measles, but can be controlled by an antihistaminic such as promethazine hydrochloride, given for 10 days. The drug may also cause the unique hyperplasia of the gums, especially in children, macrocytosis, or rarely macrocytic anaemia, gastric disturbances, and most commonly ataxia, incoordination, and diplopia. It is wise to give patients having phenytoin crude vitamin B as "bemax" or "marmite"; to encourage dental hygiene; and to reduce treatment for two days from time to time if the patient becomes unsteady. Indigestion is relieved by giving the drug with meals, or with sodium bicarbonate. More serious, though rare, complications such as exfoliative dermatitis call for its immediate withdrawal, but there is no need to carry out repeated blood counts.

Methoin (mesontoin, or methyl-phenyl-ethyl-hydantoinate) has the same dose and similar therapeutic effect. It does not cause gum hypertrophy, but may make the patient drowsy, and is more likely to cause blood changes than is phenytoin sodium. It can be given as an alternative when gingivitis is troublesome.

It is so useful to give the hydantoins and phenobarbitone together that they can be obtained in the same capsule—phenobarbitone 0.05 g. and phenytoin sodium 0.1 g., to be given two or three times a day.

Primidone

Primidone (mysoline) has been successful in major epilepsy where other anticonvulsants have failed. It is not often toxic, but it has a sedative action, particularly when given with phenobarbitone, so that I never use these two substances together. Primidone is still much more expensive than the anticonvulsants already mentioned, so it is sensible to use phenobarbitone and phenytoin before trying it. Begin with very small doses indeed, gradually increasing from half a 0.25-g. tablet to three or more a day, because some people tolerate it very badly, are drowsy, ataxic, and may have vertigo and vomiting.

Once established, treatment with primidone seems uneventful. It can, with benefit, be combined with phenytoin, particularly in major epilepsy, but it is unlikely to be so successful with focal attacks, or minor attacks of any kind.

Treatment of Petit Mal

True petit mal is much more difficult to treat successfully than are other forms of epilepsy. Fortunately, however, unless the short attacks are very frequent, they may be no more than a nuisance, and a child may live in reasonable adjustment to them. In consequence, if attacks are resistant to treatment or the patient intolerant of it, it may be expedient to cease, letting the child continue otherwise normally, as an alternative to a drugged life.

The substances so far mentioned are usually of little value in treating true petit mal, though some brief "absences" may really be unrecognized focal attacks, and so respond to phenobarbitone or phenytoin. In general, sedatives make true petit mal worse, and stimulants improve it. In addition, children with petit mal are apt to become aggressive, surly, and unsocial with phenobarbitone, and so have more attacks. Conversely, amphetamine, dextroamphetamine, and caffeine may greatly benefit patients with petit mal and improve their behaviour. It is important in view of the specificity of treatment to be guided by the electroencephalogram as well as by the characteristics of the attacks.

Diones

Troxidone (tridione) is sometimes drastically successful in controlling petit mal. When it is successful it seems to work in quite a small dose, and increasing the dose does not improve the therapeutic response. Adults or large children can take three or four 0.3-g. tablets a day, smaller children three or more 0.15-g. tablets according to size.

Many patients have toxic responses, but fortunately these are usually not serious. Most commonly there is glaring vision, when objects glow and sparkle in bright light, while hiccups or nausea also occur; but these symptoms do not often call for withdrawal of the drug. Rashes may be seen initially but often subside; occasionally blood dyscrasias occur—aplastic anaemia and granulopenia. It is much more important to watch the child's health than to do frequent blood counts, because harmless fluctuations in the count may be encountered and a sudden aplasia missed. I give special attention to details of health and do not do serial blood counts, and so far have been able to regulate treatment without harm to the child. If troxidone is moderately successful, see if paramethadione (paradione) in the same dose is better, otherwise stop treatment.

Other Drugs

Amphetamine.—Amphetamine sulphate, methylamphetamine, or dextroamphetamine, 5 mg., may be effective in true petit mal. They may reduce attacks and improve the child's behaviour. They should be tried if petit mal is frequent, and children tolerate them well. Methylamphetamine has the fewest side-effects. Caffeine citrate 5 gr. (0.32 g.) may help children benefited by amphetamine.

Acetazolamide (diamox) has recently been given with other anticonvulsants because, as well as being a diuretic, it is a carbonic anhydrase inhibitor and lowers blood *p*H. Reports have varied, and results are often disappointing, but occasionally the addition of acetazolamide (0.25 g. once or twice a day) to existing anticonvulsants has been followed by striking improvement. There are minor toxic effects, and rare serious ones. Acetazolamide is expensive, but a short trial of its effects will quickly establish its value in any one case.

Phenacemide (phenurone) 0.5 g. one to three times a day has serious toxic effects. This is a great pity, because it is a most effective agent in all forms of epilepsy. Frequently, there is improvement in the refractory case, to be followed by anorexia, nausea, liver damage, or blood disorder. It also causes psychosis. It should, I think, be used only as a last resort when attacks are out of control and the patient is under close observation.

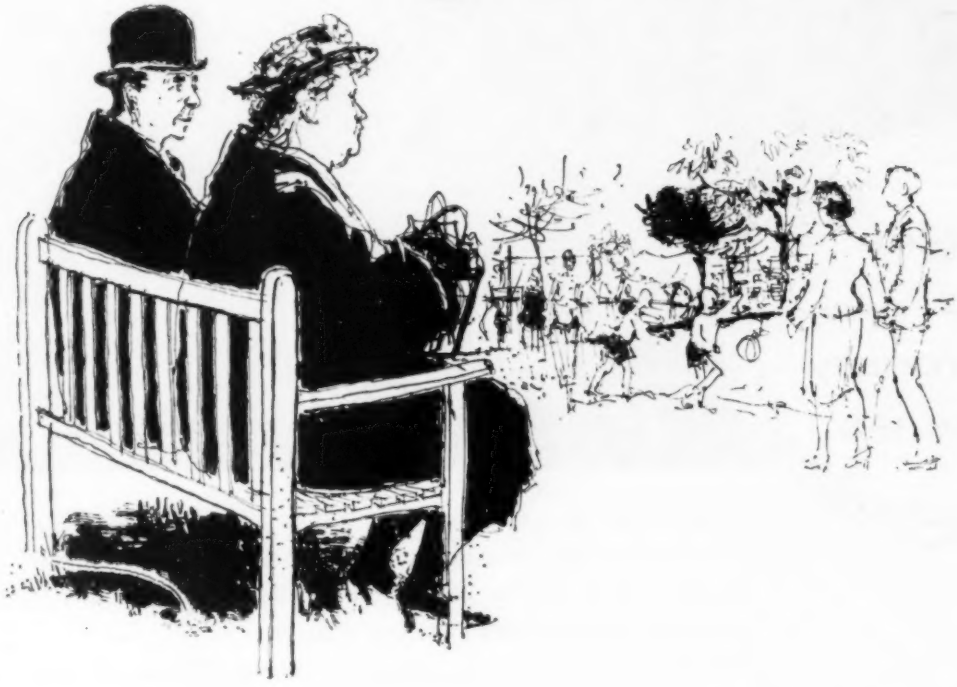
Among other substances, *phensuximide* (milontin) 0.5 g. three to four times a day is the most well tried. It is effective in petit mal epilepsy, and can be tried after the substances already mentioned.

A final note of warning. If several drugs have been tried, and more than two are being used, the patient is probably suffering more than he is gaining by them.

Status epilepticus remains a very dangerous complication which must be brought under control as soon as possible. Paraldehyde (5 ml. intramuscularly) repeated every two or three hours until attacks have stopped is probably still the safest drug. Intravenous anaesthesia can also be used, but an anaesthetist with positive-pressure apparatus should be available.

A new adjunct to geriatric care

'JUVEL'



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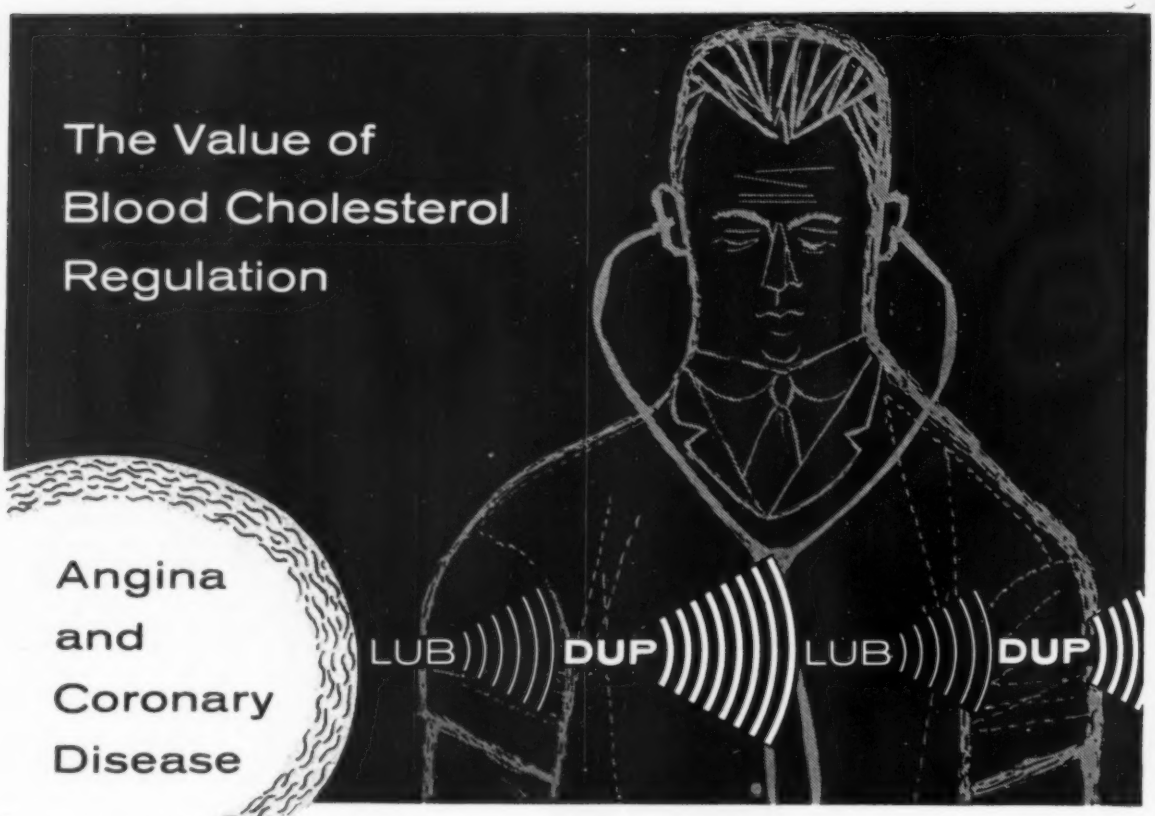

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INSTITUTE OF ORTHOPAEDICS

OPENING OF NEW RESEARCH LABORATORIES

On October 31 Sir HENRY DALE, O.M., F.R.S., on behalf of the Wellcome Trustees, opened a new research block for the Institute of Orthopaedics (London University). The block is at Stanmore, where the country section of the Royal National Orthopaedic Hospital is located. The Wellcome Trustees had given £43,000 towards the building and London University about £20,000. Sir HENRY FLOYD, chairman of the Hospital, presided over a distinguished company which included Lord COTTESLOE, chairman of the North-west Metropolitan Board, Sir FRANCIS FRASER, director of the British Postgraduate Medical Federation, and Mr. H. J. SEDDON and Mr. H. JACKSON BURROWS, director and dean, respectively, of the Institute.

Development of the Institute

The Institute of Orthopaedics was established in 1946, under the aegis of the British Postgraduate Medical Federation. At first, the only accommodation available was that provided by the Royal National Orthopaedic Hospital : one floor of the town section at Great Portland Street was converted into laboratories, a lecture-room, and a library ; and laboratories for clinical pathology and bacteriology were provided at the country section at Stanmore, where an animal house was erected. In 1951 a metabolic unit was opened, and London University approved a scheme for the erection of an H-shaped laboratory building at Stanmore. Money was provided for the first wing and a department of biochemistry was opened in 1952. During the next two years the laboratories for morbid anatomy and for clinical research at the town section were extended, and the Wellcome Trustees provided £2,000 for the equipment of an orthopaedic museum.

The opening of the research block at Stanmore represents the completion of the Institute's plan. The new building has four sections. Biochemistry is already well established under the direction of Dr. P. G. WALKER, who is engaged in the investigation of enzymes concerned in the breakdown of hyaluronic acid and chondroitin sulphate. Of the new sections one is for the housing of experimental animals. Another wing is devoted entirely to clinical pathology and bacteriology, where Dr. CHARLES LACK is engaged in a number of investigations which include the preparation of plasminogen, the preparation and characteristics of staphylokinase, serological tests for staphylococcal infection, the action of plasmin on cartilage, and the mechanism of the destruction of cartilage in suppurative arthritis. The fourth wing, for clinical research, contains a combined common-room, lecture-room, and library, a viewing-room for studying series of radiographs, and three laboratories, one of which is already occupied by Dr. ANGUS MCPHERSON, who is working on visceral-somatic spinal reflexes. The old bacteriological laboratory has been converted into a small department of experimental surgery and has been named after Sir Henry Dale. There will now be ample opportunity for registrars and clinical research assistants to carry out modest investigations under the guidance of senior workers.

The department of morbid anatomy at Great Portland Street, under Dr. HUBERT SISSONS, who has made a particular study of bone disorders and of muscle atrophy, will be able to spread a little into the department of experimental surgery at the country hospital. Also at Stanmore, Dr. JOHN SCALES has built up a department of biomechanics and surgical materials. He is concerned with the fate of metallic implants in the body, the design of prostheses, and the applications of plastics in orthopaedics. Finally Dr. REGINALD NASSIM is directing a study of bone disorders, jointly with the hospital, in a metabolic ward.

London as a Postgraduate Centre

Speaking at the opening ceremony, Sir HENRY DALE said it was indeed a pleasure for him and his fellow trustees to see for themselves how much had been achieved with the grant they had been able to make from the Wellcome Trust. He had no doubt that the decision of the University of London to develop and organize the facilities offered by the great metropolis and its hospitals for medical education at an advanced postgraduate stage was a step of the greatest importance for the progressive use of medical knowledge, now advancing with such impressive rapidity. Orthopaedics had enjoyed during the past half-century, and especially during its more recent decades, at least as great and even dramatic a development in the range of its possibilities, and in the effectiveness of its methods, as had any of the other major departments of medicine and surgery. It had given them, accordingly, a special pleasure to be able to do something to assist the further and even more rapid advance of the subject.

Mr. SEDDON then thanked Sir Henry Dale for opening the building, and proceeded to describe the various departments.

BRITISH ORTHOPAEDIC ASSOCIATION

AUTUMN MEETING AT OXFORD

The fortieth annual meeting of the British Orthopaedic Association was held from October 2 to 4 at the Nuffield Orthopaedic Centre, Oxford, under the presidency of Mr. NORMAN CAPENER. After the usual instructional course on the first day, a number of papers were read, some of which are summarized here. Sir HARRY PLATT made the meeting memorable by delivering the first Founders' Lecture. Taking the title "Quick, Thy Tablets, Memory!" he described the association's origins and the great figures connected with its foundation forty years ago.

Bone Growth

Professor J. TRUETA (Oxford) said that he and his colleagues had collected data suggesting the main function of the blood vessels reaching the growth-plate from its epiphysial side was to nourish the repeatedly dividing cartilage cells, whereas the peculiarly arranged vessels underlying the metaphysial side of the plate were mainly, and perhaps only, concerned with the calcification of the giant cartilage cells. Interruption of these metaphysial vessels, or their occlusion by pressure, caused a total failure not only of calcification but also of the degeneration of the giant cells. The picture was radiographically and histologically similar to rickets.

Mr. J. D. MORGAN (Oxford) said the epiphysial plate matured only when ossification of the shaft had extended sufficiently to form the metaphysial end-plate, subsequent growth being in the direction of the cartilage-cell columns which formed at right angles to the base of the plate. At the upper end of the femur the metaphysial end-plate was wedge-shaped, growth in length being proportional to the angle formed and probably at first equal to that at the lower end. The two sides of the wedge eventually separated as the epiphyses for the head and greater trochanter developed, but at first most of the growth in length came from the capital side, resulting in the coxa valga normal in infancy which persisted if the trochanteric epiphysis for any reason closed prematurely. If the capital epiphysis closed early from congenital deformity, injury, infection, or paralysis, the trochanteric epiphysis took over control of longitudinal growth, and any operative procedures in such circumstances must therefore avoid damaging the latter. It was only if both parts were closed that gross shortening occurred. At the lower end interruption of growth commonly affected only part of the epiphysial plate, resulting in both shortening and distortion of the bone. Ischaemia, as in Perthes's disease, promoted growth in circumference of the epiphysis and hence widening of the bone. Disuse of the lesser trochanter, as in iliopsoas paralysis, resulted in failure of this area of the shaft to thicken normally.

Intrauterine Fracture and Congenital Coxa Vara

Mr. E. W. SOMERVILLE (Oxford) discussed congenital coxa vara, basing his argument on an example in which the mother had injured her abdomen six weeks before term. At

eight months of age the capital epiphysial centre had first become visible radiographically, in its normal position, together with a "ghost" of the missing neck, the upper femoral shaft lying at an angle to the bony lower part of the shaft. Arthrogram and exploration confirmed these findings, which he considered to be due to an intrauterine fracture of the cartilaginous femur. As a result primary ossification of the shaft, depending on its nutrient artery and the capillary loops formed from it, had been brought to a halt at the site of the fracture, and the metaphysial region had failed to ossify. In such circumstances an epiphysial plate did not develop, but ossification proceeded normally in the ossific centres of the head and great trochanter where the blood supply was intact, and spread unhindered into the metaphysial region. Here, later, irregular ossification occurred, and growth in length at the upper end of the femur was no longer possible.

Sir REGINALD WATSON-JONES (London) supported Mr. Somerville, and thought that this and similar conditions in this region were all due to birth fractures through cartilage. Mr. DAVID TREVOR (London) asked why, if that were so, the condition was so commonly bilateral, and Mr. J. C. SCOTT (Oxford) asked for an explanation of the frequent association of other congenital defects and of a familial incidence. Mr. SOMERVILLE agreed that many instances were not explicable as fractures, but thought that basically the underlying abnormality was one affecting the local blood supply rather than the cartilage itself.

Tendon Grafts and Tenolysis

Professor PAUL BRAND (Vellore) illustrated his contribution on the principles of free tendon-grafting with a film of outstanding quality showing the removal of a plantaris graft and its use in his operation for intrinsic paralysis of the hand. The principles he so convincingly propounded he summarized as follows: Tendon transfers are more regularly successful than free tendon-grafts because they have no suture line in the length of the tendon to cause adhesions, and because they carry their own blood supply and therefore do not need to grow new blood vessels which attach them to surrounding structures along their length. Frequently, however, it is difficult to spare a muscle with a long enough tendon without causing a secondary disability. In such cases a free tendon-graft from a more proximal muscle may be necessary. Secondary deformities following the Bunnell sublimis operation had led him to use a new operation, taking free grafts from a wrist-moving muscle. During the carrying out of 200 free tendon-graft operations for intrinsic paralysis of the hand they had worked out new methods which had improved the effectiveness of the grafts by minimizing the formation of adhesions. The ideal material for free grafts was the plantaris tendon. After giving the details of his method, Professor Brand then described a new operation for intrinsic paralysis of the hand. This involved the use of the extensor carpi radialis longus or brevis muscle, extended by four tendon-grafts through the interosseous spaces of the hand, anterior to the transverse metacarpal ligaments, which were inserted at the edge of the dorsal expansion of each finger.

Professor J. I. P. JAMES (Edinburgh) described his use of cortisone in tenolysis. Assuming that Carstam's work on the effectiveness of cortisone in preventing tendon adhesions in rabbits might be applicable to man, and after disappointing results with a small series of tenolyses without cortisone, Professor James had used corticotrophin or cortisone, starting treatment two days before operation and continuing it for 14 days post-operatively. The dosage he now used was 150 mg. of cortisone daily, with weaning afterwards and the usual precautions for steroid therapy. Dressings were changed after two days and active exercises then started: sepsis had not been a problem. Although there had been some failures, in a series of 22 patients the results were on the whole strikingly better than in cases done without cortisone. He had not been impressed that cortisone had helped in the few cases of tendon-grafting he had done under its cover.

Bone Grafts for Malposition and Non-union

Mr. R. G. TAYLOR (Oxford) reviewed 72 bone grafts performed between 1950 and 1955 for fractures of the shaft of long bones. Two-thirds were done because of fibrous union, and the remainder early for malunion, at an average period of three weeks after the fracture. If closed reduction failed or needed repeating more than 10 days after the fracture, Mr. Taylor considered open reduction and fixation by grafting to be usually the method of choice. In analysing the causes of fibrous union he noted that no case had occurred in 200 consecutive tibial shaft fractures, both simple and compound, in patients under 17; over this age the age of the patient was not a factor, nor was the site of fracture. Two-thirds of the failures to unite by bone had occurred in compound fractures, although these made up less than one-third of the total fractures seen. The severity of the injury, the amount of bone and skin lost, and infection were all factors making fibrous union more likely. Repeated manipulations after the tenth day were particularly harmful in this connexion, as was also distraction from any cause. He recommended the use of a combined onlay and inlay graft, the latter being firmly fixed with four screws. The fibrous zone was resected only if the bone ends needed realignment. In the 72 grafts there had been eight infections, of which seven occurred in previously compound fractures, and among these were the only two failures to produce bony union. The average period of total immobilization for tibial grafts was 104 days, with a further 40 days in a gaiter for two-thirds of them.

Vascular Occlusion Causing Backache

Dr. DAVID L. FILTZER (Baltimore) discussed vascular insufficiency as a cause of low back pain. He reviewed 50 cases that had been under the care of Dr. Bahnson at the Johns Hopkins Hospital, of which 43 were in males. All had suffered occlusion of the lower aorta or the common iliac arteries, and 22% had had back pain of major or minor degree. In many a multiplicity of other diagnoses had been made before the correct diagnosis. All 50 had been proved by aortography and/or operation for endarterectomy or replacement by a homograft, procedures which had relieved back pain if it was present. Dr. Filtzer stressed that a tentative diagnosis of vascular insufficiency should be considered in every patient with backache, and emphasized particularly the importance of the history.

Other Contributions

Other papers were read by Mr. D. M. BROOKS (London) and Dr. A. ZAOUISSIS (Athens) on arthrodesis of the shoulder for paralysis of the upper limb, Mr. W. DE WYTT (Dublin) on a review of 45 cases of anterior vertebral fusion, Dr. J. CHALMERS (Chicago) and Dr. H. A. SISSONS (London) on an experimental comparison of bone-grafting materials in the dog, Mr. MICHAEL SQUIRE (Reading) on carpal mechanics and trauma, Mr. G. K. ROSE (Shrewsbury) on correction of the pronated foot, Mr. J. PIGGOT (Exeter) on dislocation of the hip in children, and Mr. J. W. DICKSON (Sheffield) on ectopic ossification in paraplegia. In addition there were clinical and scientific demonstrations at the Nuffield Orthopaedic Centre.

Motoring News

EARL'S COURT MOTOR SHOW

This year's Motor Show at Earl's Court was one of the most disappointing in recent years for the popular-car motorist. Several new models were available for buyers in the luxury class, but for under £1,000 the average family motorist would have found little to excite him, with the possible exception of the Austin A40. It is likely, however, that further popular models will appear within the next three or four months.

One group which showed promise this year was the ultra-lightweight range of two-cylinder models of up to 5 h.p.

The diminutive DAF from Holland, using a two-cylinder two-stroke power unit of 600 c.c., was worth admiring. Its interior was particularly well appointed and gave an atmosphere of comfort which befitted a larger car. Of similar dimensions was the new Goggomobil Royal. A native of Bavaria, the Goggomobil is a popular German economy car produced in large quantities, and this latest model, the Royal, now gives adequate comfort for four passengers for short journeys, and costs £710. It cannot, however, be called good value when compared with other British cars, but this is the price the buyer has to pay for individuality and, of course, economy. Likewise the British Berkeley, now with an alternative saloon model at £725, caters for the family motorist—albeit one with a very tiny family. Some more small newcomers were the N.S.U. Prinz and the Sport Prinz, the latter being a smart 85 m.p.h., 50 m.p.g., close-coupled saloon; the streamlined Friskysprint with 492 c.c. two-stroke engine by Excelsior, giving it a top speed of 90 m.p.h.; and the Stirling Opperman, made by the Unicar concern at Stirling Corner, near Elstree. This last is a new venture by this firm, and at £541 it may well capture one of the few small spaces left in the low-price group for an effective family runabout. With a 424 c.c. power unit it can offer 50 m.p.g. petrol consumption and accommodation for two adults and two children.

Larger models recently introduced and costing over £1,000 were the Aston Martin DB4, Humber Super Snipe, Rover 3-litre, Armstrong Siddeley Star, Bristol 426, Daimler Majestic, Mark IV Jaguar, twin-cam M.G.A., and the Peerless. Of these the Rover retains its characteristics as a "quality" car, although one which has lost some of the dignity of its smaller brothers, especially with regard to interior appointments, the instrument panel in particular. The Humber Super Snipe offers supreme luxury at a moderate price, but it still inherits the traditional Rootes Group body shape. Models with disk brakes are the latest Jaguar, the Mark IX, the twin-cam M.G.A., the Aston Martin DB4, the Bristol 406, the Daimler Majestic, and the Armstrong Siddeley Star, which has them on the front wheels only. All these models were new to Earl's Court on this occasion, having been introduced in the course of the past year.

The Jaguar Mark IX is a more powerful version of the current model, as is the 1½-litre M.G.A. The Aston Martin, the Bristol, and the Daimler are recent introductions. The Armstrong Siddeley Star is similar in appearance to the popular Sapphire but is fitted with a larger engine, now of 4 litres capacity, and incorporates many other detailed improvements.

The Austin A40 was one of the very few really new cars at the Show, being a further addition to the already extensive B.M.C. range. Unique in design, having done away with the external luggage boot, it is a good buy at £676 for the small-car motorist. But it is a small car. Rear seat accommodation is limited, and the headroom barely adequate for a tall passenger. The whole seat folds to allow considerable quantities of luggage to be carried, but the opening flap is small by reason of the large fixed window above it, thus preventing bulky objects from being carried.

In the caravan section there were few revolutionary developments with the exception of motor caravans, which are rapidly coming into fashion. Such vehicles obviate the need for towing the conventional caravan at 30 m.p.h., in Britain anyway, and they are no more expensive to transport on boats or trains than conventional cars. They are also easy to manipulate in confined spaces. Martin Walter Ltd., of Folkestone, one of the largest firms in this field, convert Bedford and Ford vans, in particular, into comfortable two- and four-berth sleeping wagons with built-in cooking and washing facilities. Similar conversions are available on Volkswagen, Morris, and Austin chassis. No purchase tax is payable on vehicles of this sort, with the result that they represent excellent value for money.

New in the accessory line were Ward's pistol-grip spot-lamp for fixing to the windscreen pillar, the Continental-shaped wing mirror, and the folding camp chair by Desmo, the new Lucas S7 battery with one-piece venting system instead of the customary removable plugs, coloured Dunlopillo cushions which fold, and a range of new small lamps by Marchal which can be used either as flashing indicators, side lamps, or fog lamps. A gayer touch has been given to many of the cars now on the market by the use of new pastel colours and two-tone schemes. Further varieties of leathercloth add more charm to interiors, while ribbed rubber and rubber-backed materials are appearing more and more on the floors of current popular models.

Technically this was not a very interesting exhibition, with most makers sticking to their well-tried power units and chassis layouts. Britain, however, leads the world with the disk brake, and it is likely that within a very few years these will be available on mass-produced models. Improved performance has been achieved by simply enlarging the capacities of present engines instead of redesigning the units to give additional B.H.P. on the same number of c.c.s. This policy of consolidation in the motor industry has certain advantages. The longer a model is in production and the more improvements which are incorporated into it the better it becomes, and the longer it stays on the production line the more money it earns for its company. This in turn allows the designers more time to develop their new models, and we shall look forward to these appearing soon in the low-price markets in time for buyers to take advantage of the recent hire-purchase rearrangements.

IAIN GELLATLY.

Nova et Vetera

"AH, MY OLD FRIEND DR. HARVEY"

The life of William Harvey has been studied for three centuries, and it might be imagined that little new could be said. It is interesting, therefore, to note that within the last few years fresh information has been published on the subject in this country and abroad, stimulated in part by the preparations for the celebration in 1957 of the tercentenary of Harvey's death. Among these contributions the following may be mentioned.

The discovery of the Harveian Oration for 1662, in all probability by Sir Charles Scarburgh, records a tribute from a pupil to Harvey's ideals, knowledge, and zeal for investigation.[1] The account of Harvey's knowledge of neurology and psychiatry, gathered by Drs. Richard Hunter and Ida Macalpine,[2] reveals another side of Harvey's inquiring mind. The recent find among the muniments at Hatfield of the letter, dated 1605, from Dr. Lancelot Browne recommending his son-in-law, Dr. William Harvey, for the post of physician at the Tower of London indicates how early his professional talents were appreciated.[3] The letter of Bishop Brian Duppa to Sir Justinian Isham of 1657 relates that Harvey paid attention to dietetics and nutrition and "would sometimes fast two dayes together"; that the bishop was with him the day before he died; and that Harvey's life "went out like a spark, without any violence or noise at all."[4, 5] In 1956 Dr. F. N. L. Poynter discovered in the poems of Dr. John Collop, published in 1656, a contemporary poem on Harvey of some merit.[6] We have had new and better English translations of *De motu cordis*[7] and of *De circulatione sanguinis*—the two anatomical essays addressed by Harvey in 1649 to Jean Riolan, jun.[8]—from the pen of Dr. K. J. Franklin, which only one who is at the same time physiologist, classical scholar, and medical historian could have achieved; and Dr. Louis Chauvois has published simultaneously in French and English a new life of Harvey.[9] It is an impressive catalogue of biographical information, but the harvest is not yet exhausted.

Sir Geoffrey Keynes, who can equally delight and instruct us in new paths in surgery and in medical history, iconography, and English literature and poetry, is a leading authority on William Harvey. He is also a Fellow of the Royal College of Physicians, and his Harveian Oration[10]

for 1958 to the College is entitled: "Harvey through John Aubrey's Eyes." Sir Geoffrey, in studying Harvey's life, takes up the torch handed from Sir D'Arcy Power, who like him was a surgeon at St. Bartholomew's Hospital, Harvey's hospital. Sir Geoffrey reminds us that Harvey, like many of his contemporaries, practised surgery as well as medicine—he bequeathed to Sir Charles Scarburgh all his little silver instruments of surgery. As Sir Thomas Barlow said in his Harveian Oration[11]:

> "I think we may rest content that our Harvey, who was universally admitted to be a great anatomist and naturalist, was also an experienced pathologist, a learned physician, and that he had the qualifications of a good all-round medical practitioner."

Aubrey's Picture

It is John Aubrey (1626–97), that prince of gossiping biographers, "with an unerring instinct for the telling detail," who in the *Brief Lives*[12] gives a vivid picture of Harvey's later years and of his personality. He had seen Harvey at Oxford in 1642, but it was not until 1651 that he became his friend. He is the only recorder of what Harvey looked like, of what he said, of his personal habits and foibles, and of the manner of his death. "Ah, my old friend, Dr. Harvey, I knew him right well!" he wrote. Aubrey was odd, irrelevant, and unsystematic, but he had a talent for description, an excellent memory, and desired to tell the unvarnished truth. Sir Geoffrey emphasizes these qualities of Aubrey as he proceeds to examine his word-portraiture of William Harvey. Many writers on Harvey have used Aubrey's account, but in their "pilfering" have thrown doubt on his veracity. "A gossip, inaccurate and irrelevant," are some of the epithets applied to him. Can we trust his account of Harvey?

William Harvey's treatment was considerably in advance of his time. He prescribed the accustomed Galenical remedies, but was often sceptical as to their efficacy. In the case of Prince Maurice, who was suffering from a slow fever, Harvey stated that he and his colleagues resolved to give "very little physic, only a regular diet and cordial antidotes." The Prince made a good recovery. It was this scepticism, suggests Sir Geoffrey, that made Aubrey, while praising Harvey as an anatomist, consider him a bad physician, although he treasured his prescriptions, which are with his other papers in the British Museum. Aubrey certainly erred, after conceding that Harvey understood Latin and Greek pretty well, when he said that "he was no Critique, and he wrote very bad Latin. The *Circuitis Sanguinis* was, I take it, done into Latin by Sir George Ent." Of the truth of this statement there is no evidence, and, as regards Harvey's classical knowledge, Dr. Franklin has conclusively shown that he wrote scholarly Latin and that in translating his Latin into English passages can be discovered which are beautiful in either language. Harvey could write good English too, for in addition to his many great talents he was a man of letters. Sir Geoffrey suggests that it may have been a sight of the manuscript of Harvey's *De Motu Locali Animalium*, rough notes, which in spite of bad handwriting, abbreviations, and additions Dr. Gweneth Whitteridge, at the instance of the College of Physicians, has at length triumphantly translated and interpreted, which led Aubrey to decry Harvey's Latinity.

With the exceptions just mentioned, Sir Geoffrey Keynes finds that most of Aubrey's statements concerning Harvey are supported by additional evidence, such as that of Mrs. Harvey, his great-niece, who told Dr. Heberden of his oddities and foibles. Aubrey observed also Harvey's modesty about himself and his discoveries, his accessibility to younger men and his encouragement of them, which the Harveian Oration of Sir Charles Scarburgh corroborates. Doubt has been thrown upon Aubrey's anecdote of Harvey being entrusted with the care of the young princes, Charles and James, at the battle of Edgehill in 1642.[13] Sir Geoffrey, examining the evidence, shows that the account of the battle by an anonymous writer agrees with Aubrey's

(Continued at foot of next column)

(Continued from preceding column)

account; and it is strengthened by the portrait of the two princes at the battle which King Charles I presented to Harvey, no doubt to commemorate the occasion. The picture, for many years in the possession of the Harvey family, is now in the Scottish National Portrait Gallery in Edinburgh. Finally, "Aubrey's description of Harvey's last hours bears the stamp of truth."

After a searching examination, Sir Geoffrey Keynes considers that Aubrey's picture of William Harvey is in the main an accurate one, though his natural inclinations sometimes led him to misinterpret certain of Harvey's qualities. He concludes that Aubrey has bequeathed to us the most lifelike portrait of Harvey that we possess.

In this memorable Harveian Oration, with much learning and investigation, Sir Geoffrey Keynes has brought out for the first time the highlights of Aubrey's portrait of Harvey. In doing this he has not only justified Aubrey's veracity, but has made us see the great and good Harvey through John Aubrey's eyes.

ARTHUR S. MACNALTY.

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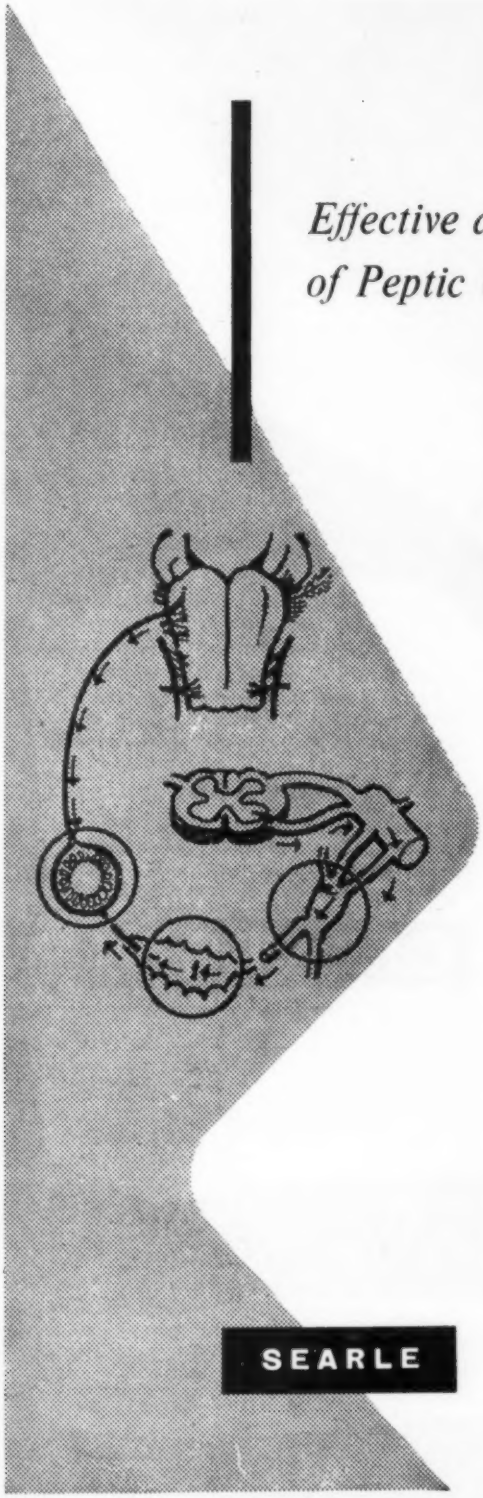

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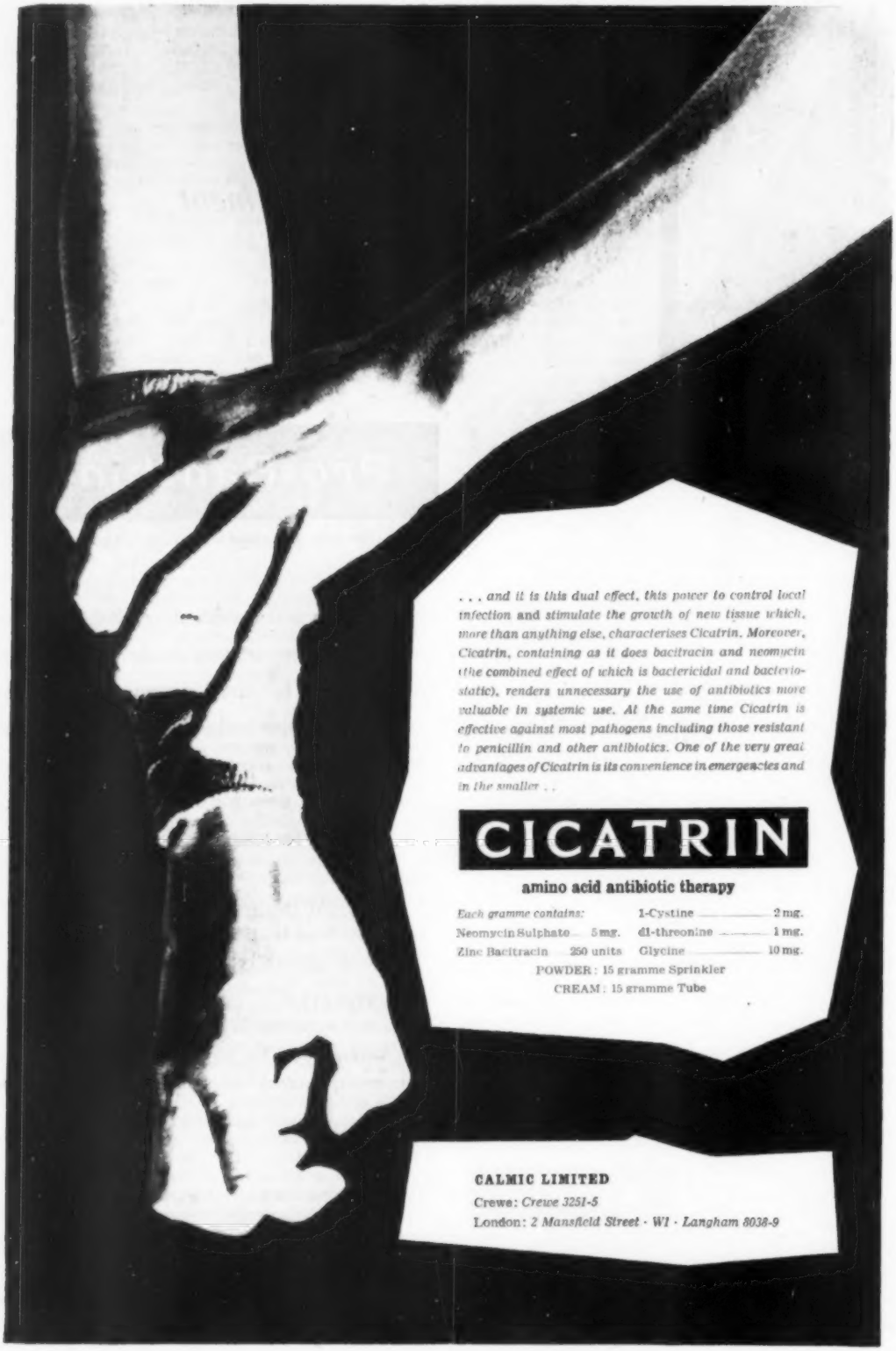
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Correspondence

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Addiction to Unrestricted Drugs

SIR,—The communication from Drs. C. P. Seager and A. R. Foster (*Journal*, October 18, p. 950) describes seven addicts to chlorodyne, methylpentynol, preludin, or carbromal, all being psychopaths. They state that in three patients taking carbromal there was evidence of physical dependence, but do not describe the symptoms and signs to support this. If carbromal really does cause physical dependence it is of the greatest importance that this should be clearly established, and I hope that the writers will provide the evidence.

Their conclusion that all drugs which have a euphoriant or sedative action should be included in Schedule 4 of the Poisons Rules is alarming. If their view were adopted, to be consistent, we should also include the far more noxious and enjoyable drugs—alcohol and tobacco. We should, I suggest, think very carefully before recommending restrictions to legislators which would inevitably involve the practitioner in yet more work and which would do but little to protect a relatively small number of psychopaths.—I am, etc.,

London, W.1. A. H. DOUTHWAITE.

SIR,—I read with much interest the timely article by Drs. C. P. Seager and A. R. Foster (*Journal*, October 18, p. 950). The dangers attendant upon the unrestricted sale of "persomnia" are well illustrated by the following case, recently under my care.

An intelligent male, aged 39, suffering from recurrent bouts of depression, had been addicted to persomnia for several years, consuming on an average about half a tin—16–20 tablets daily. Following a suicidal attempt in which he took 56 tablets over two days, he was admitted to an observation ward in a stuporous condition, showing a blood bromide level of 120 mg./100 ml. On becoming rational he expressed the desire to be cured of addiction, and was admitted to this hospital as a voluntary patient. After some two months, during which time he received electroplexy for his depression, followed by intensive supportive psychotherapy, he announced that he felt much improved and no longer had any craving for persomnia. However, while on a pass to seek employment, he procured a further supply of persomnia tablets, taking 14, and just managed to stagger to the hospital gates in a drowsy condition which necessitated a stomach wash-out. He again improved, and expressed appreciation for the opportunity to remain in hospital for a while, without passes and the temptation to obtain more persomnia.

The difficulties in treating this type of case seem to be immeasurably increased when the patient has unlimited access to the drug of his addiction, and it is possible that such people may never obtain relief until this and similar habit-forming dangerous drugs are placed on Schedule 4. Also advertisements in the national press and on independent television appear to have resulted in the widespread use of persomnia, as judged by the numbers of patients encountered in one's psychiatric practice who regularly take this preparation. Under such circumstances their treatment with orthodox medicines is rendered a complex and even dangerous undertaking. I therefore propose a speedy revision of the Poisons Rules whereby persomnia, and indeed some of the other drugs referred to by Drs. Seager and Foster, would not be obtainable without a doctor's prescription.—I am, etc.,

Banstead Hospital, Sutton. J. C. BARKER.

SIR,—The suggestion in the paper by Drs. C. P. Seager and A. R. Foster on "Addiction to Unrestricted Drugs" (*Journal*, October 18, p. 950) that "drugs which have euphoriant or sedative action should be placed on the list of Schedule 4 Poisons," and hence be obtainable only on prescription, is wise and timely.

For some time I have noted with concern evidence that a group of hypnotics, the open-chain ureides—carbromal and bromvaletone, and particularly the former—were being increasingly used for self-medication, and that they could produce addiction. Carbromal has long been considered by the medical profession and by pharmacologists to be a safe hypnotic, which indeed it is when administered under medical supervision. A new situation arose when proprietary preparations containing carbromal were widely advertised to the public through the national press as a "safe sedative." These preparations can be bought freely by the public in pharmacies and in some drug stores. It becomes increasingly obvious that the terms "safe" and "hypnotic" are contradictory where self-medication is concerned, for if one tablet is good then half a dozen are so often considered to be six times as good.

Instances of addiction or habituation to drugs such as carbromal are not easy to obtain; and are probably more readily available to the psychiatrist and general practitioner than the general physician. Three instances of carbromal addiction are reported in the paper by Drs. Seager and Foster. In personal communications Professor Aubrey Lewis was able to quote six instances of carbromal addiction under treatment at the Maudsley Hospital, and Dr. L. C. Cook four patients treated for this condition at Bexley Hospital.

A typical instance came under my care recently. Mrs. E. H., aged 51, was admitted deeply unconscious, having taken about 20 "persomnia" tablets (a preparation containing carbromal and bromvaletone). With energetic treatment she regained consciousness in two hours. She subsequently stated that, owing to insomnia and domestic worries, she had been taking the tablets regularly over the past three years. As indicated in advertisements in the national press, she thought they were safe. She admitted purchasing three 2s. 9d. tins of 40 tablets a week from chemists, some of whom had warned her to be cautious in taking them. She had a strong feeling of guilt and hid the tins from her husband, who was concerned about her addiction. A psychiatrist who saw her did not consider her condition psychotic. She also showed a carbromal rash on her legs.

Personal communications from four dermatologists, three on the staff of London teaching hospitals and one in a large London general hospital group, all indicated the increasing frequency of carbromal rashes. One estimated that carbromal eruptions occur three times as frequently as any other type of drug rash, two that it was the commonest drug rash seen, and the fourth that, "with the exception of penicillin, eruptions due to carbromal drug rashes were the most frequently seen in dermatological out-patient departments." E. W. Prosser Thomas[1] has recently drawn attention to the increasing incidence of carbromal rashes and lists fourteen proprietary preparations containing the drug. I had discovered fifteen. P. Borrie[2] drew attention to the condition in 1955. The rash is very distressing but not dangerous. Its high incidence indicates the extent of carbromal self-medication.

The Pharmaceutical Society of Great Britain have observed the situation with concern and in May last made the following recommendation,[3] "That the Poisons Board be informed that in the Council's view there is a prima facie case for open-chain ureides to be included in the First and Fourth Schedules to the Poisons Rules, and suggesting that an inquiry be conducted by the Ministry of Health as to the extent of the abuse of such drugs and preparations containing them." The Home Secretary subsequently announced that the Poisons Board had decided that the matter be referred to the Committee on Drug Addiction for their consideration. Pending this deliberation the Pharmaceutical Society advised pharmacists to exercise the greatest care in the supply of preparations containing these drugs.[4]

Responsible public opinion appears to be aware of the danger of indiscriminate use of sedatives. *The Times*[5] reports the National Council of Women of Great Britain as having passed a resolution at their annual conference urging the Minister of Health to prohibit the sale of "tranquillizers" to the public without a medical prescription. Tran-

quillizers in this context appear to include hypnotics. It is hoped that Ministerial and medical opinion will not lag too far behind that of the Pharmaceutical Society and the general public.—I am, etc.,

St. Alfege's Hospital, London, S.E.10. B. A. YOUNG.

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"On Call to a Nation"

SIR,—In a B.B.C. television broadcast about the National Health Service entitled "On Call to a Nation" (see *Journal*, October 25, p. 1053) a doctor was shown handing an O.S.C.1 Form to a patient and saying, "Take it (the form) to a sight-testing optician." There was no explanation either by him or in the subsequent remarks by the B.B.C. commentator that the patient had freedom of choice under the National Health Service Act to have his sight tested either by an ophthalmic medical practitioner or by an ophthalmic optician. This may have been an inadvertent omission on the speaker's part, but it is regrettable that the B.B.C. should have taken no steps to correct the misapprehension which must have been left in the minds of millions of viewers. This part of the programme therefore gave a one-sided picture at the expense of that section of the medical profession which specializes in ophthalmology.—I am, etc.,

London, W.C.1. J. N. TENNENT, Chairman, N.O.T.B. Association.

SIR,—In the recent B.B.C. television programme (see *Journal*, October 25, p. 1053) a doctor was represented as saying to a patient, "'All you need is to take it (the form) to a sight-testing optician." Section 41 of the National Health Service Act, 1946, gives freedom of choice to the patient to have his sight tested either by an ophthalmic medical practitioner or by an ophthalmic optician in the Supplementary Ophthalmic Service. It is deplorable that a doctor should be represented as virtually directing a patient to a non-medical sight-tester.—I am, etc.,

Liverpool, 1. JOHN MATTHEWS.

SIR,—The dilemma whether to present the medical profession to the public in authoritarian terms or to reduce it to the commonplace was well illustrated in the B.B.C. television programme "On Call to a Nation" (see *Journal*, October 25, p. 1053). As was to be expected, the producer alternated from one to the other. That such inconsistency is not confined to television producers was equally well illustrated towards the end of the programme. Personally, I consider that the negligence of a general practitioner failing to examine his cases is only matched by the fatuity of consultants who believe that their reassurances will allay the anxieties of patients referred to them. As is well known, only the consultant is reassured. If, however, one does believe in the efficacy of the "white coat at the desk," surely it would be more consistent not to criticize general practitioners in a programme to the public. Loss of confidence is very infectious, and patients might come to believe that even consultants can make mistakes.—I am, etc.,

London, S.W.19. L. S. GOODHARDT.

SIR,—This T.V. feature, according to your statement (*Journal*, October 25, p. 1053), depicted 57 doctors, 25 of whom had speaking parts. I saw the programme, and, as far as I could note, one woman practitioner appeared, in a non-speaking part, for about five seconds. I have not to hand the figure for the proportion of women on the *Medical Register*, but I believe that 15% is reasonably near the truth. It seems probable that, in planning the programme, the B.B.C. must have, at some stage, discussed it with the B.M.A. I suggest that the women members of the profession received, in this programme, far less recognition than that which, on a statistical basis, might have been expected.—I am, etc.,

Chester. EVELYN MARY BISKE.

Thyroid Neoplasms and Irradiation

SIR,—Professor G. M. Wilson and his colleagues in their interesting article on "Thyroid Neoplasms following Irradiation" (*Journal*, October 18, p. 929) suggest that in children the use of ^{131}I is only justifiable in exceptional circumstances and that paediatricians, among others, should appreciate the possibility of the development of carcinoma of the thyroid which has been irradiated in infancy. As far as the use of ^{131}I is concerned this has already been considered by a Subcommittee of the British Paediatric Association assisted by Dr. E. Pochin and Dr. L. Lamerton.[1] The final paragraph in the report recommended:

"That ^{131}I should not be used in children when the employment of ^{132}I would give the information which is needed. In the calculations leading to this conclusion several "safety factors" are involved which make it doubtful whether any harm will actually result from the use of small doses of ^{131}I, and it must be left to the individual paediatrician to decide whether its use is justifiable in the investigation of any specific clinical problem."

—I am, etc.,

Department of Child Health, Guy's Hospital, London, S.E.1. PHILIP EVANS, Hon. Secretary, British Paediatric Association.

REFERENCE

1 *Arch. Dis. Childh.*, 1957, **32**, 166.

Carcinomatous Arthropathy

SIR,—In his article on "Arthropathy due to Gastric Carcinoma" (*Journal*, October 25, p. 1022), Dr. E. H. O. Parry suggests that the association of these two conditions is very rare. This is probably not so. During a period of six years in Wales I saw five cases of arthropathy associated with a carcinoma, the growth being in the stomach in two cases, lungs in two cases, and the head of the pancreas in one patient. A report on the first four patients is at present in the hands of the printers awaiting publication elsewhere. Cases with finger-clubbing were excluded from my series. Multiple joint pain is, of course, a well-known symptom in association with pulmonary osteoarthropathy. In the patients that I have seen there have been episodes of pyrexia and a high E.S.R., of the order of 90–120 mm. fall in one hour (Westergren). One case, a man aged 68, was completely relieved of joint pains following a gastrectomy by Mr. Wynford Davies.

Dr. Parry is not correct in stating that there has been no previous report of gastric carcinoma causing arthropathy. Lázaro and Ramírez[1] discussed the association of multiple arthritis with malignant tumours, and mentioned two cases of carcinoma of the stomach in whom the presenting symptoms were joint pains and pyrexia.—I am, etc.,

Amersham General Hospital, Bucks. M. S. PATHY.

REFERENCE

1 Lázaro, J. P., and Ramírez, E., *Rev. clin. esp.*, 1953, **50**, 138.

Reactions after Polio Vaccine

SIR,—I was interested to read in the *Journal* (October 4, p. 835) the case report by Dr. A. Fowden on sensitivity to penicillin in British poliomyelitis vaccine. In view of my personal experiences I give herewith my own case report.

In January, 1956, whilst in Spain I developed a severe sore throat, and decided to give myself a course of penicillin, purchasing 4 vials of 400,000 units each of procaine penicillin manufactured by a well-known American firm. Prior to this I had, on several occasions, received penicillin injections without any allergic manifestations although for many years I have suffered from hay fever. I gave myself intramuscularly 400,000 units per day for three consecutive days. On the fourth day my throat was very much better, but I decided, for good measure, to give myself the last shot. Fortunately, having experienced severe allergic reactions to penicillin amongst my patients in my practice in Singapore, I always have a vial of adrenaline handy as a precaution. On this particular morning, no sooner had I injected myself and withdrawn the needle than I felt a hot flush all over my body, a tingling of the lips, and on looking at my face in

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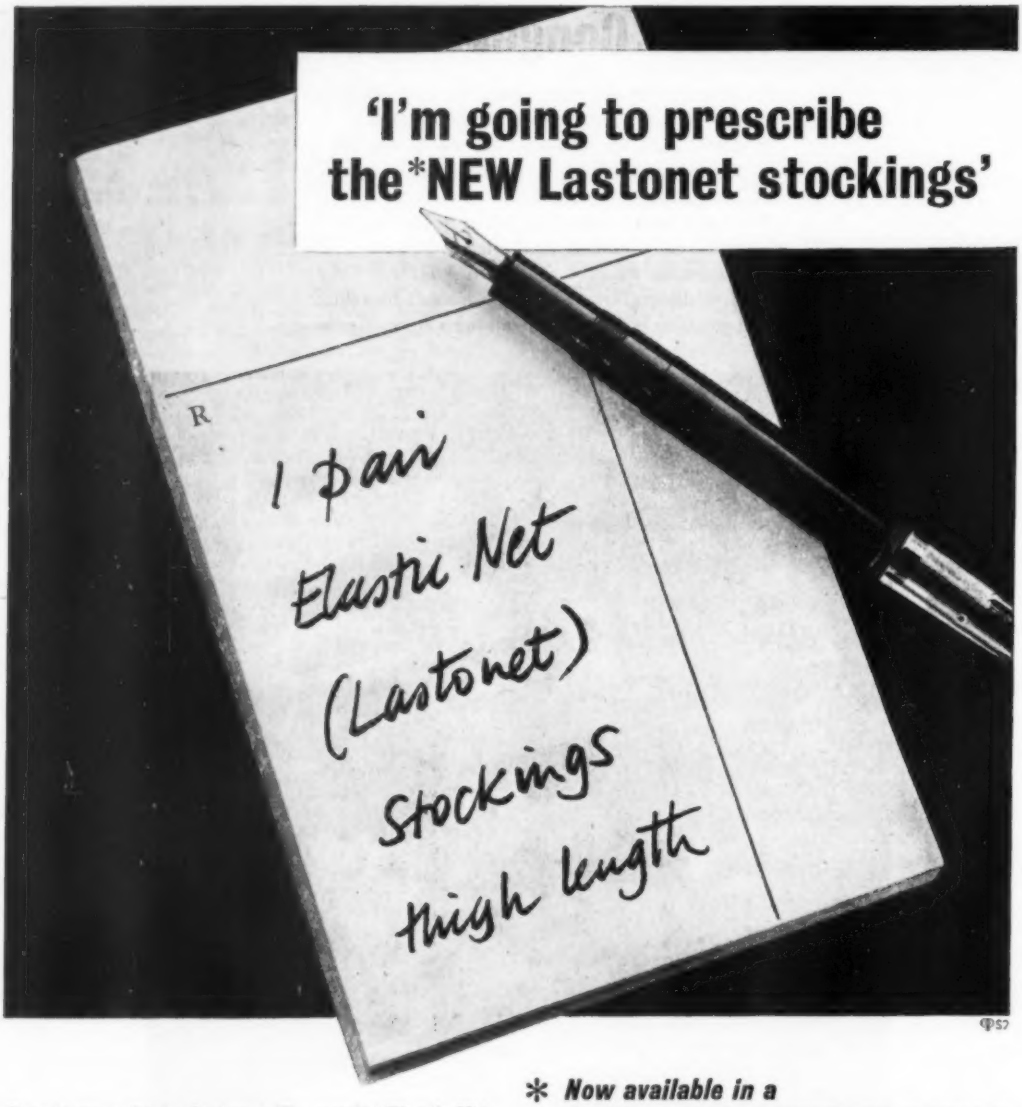

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the mirror and at my hands I saw they were deathly white. I hardly had time to shout for assistance, when I collapsed. Adrenaline was given, and for the next hour and a half I experienced a most awful sensation of doom and felt I was dying. I had a very marked tachycardia, felt cold, and was severely shocked.

Six months later I again had a severe sore throat and temperature, and commenced a course of "achromycin" (tetracycline) capsules. As a precaution, half an hour before taking the capsules I took a 100-mg. "anthisan" (mepyramine maleate) tablet. I had already taken 3 g. of the achromycin, when some 20 minutes after the last dose I experienced a flushing of the face, tingling of the lips, tachycardia, and felt cold. These symptoms subsided after two hours and I resolved never to take antibiotics again. Some time after this I ate mushrooms, and from then onwards I noticed that whenever I ate mushrooms I felt "het-up" and with it I had urgent, copious, watery diarrhoea.

On October 16, 1958, I obtained some British poliomyelitis vaccine for myself and family. On reading the essential facts about the vaccine I was a little perturbed to note that it contained a small amount of penicillin and streptomycin which the manufacturer states is almost entirely inactivated, though insignificant traces may remain in the vaccine. As a precaution, half an hour before giving myself the vaccine I took a 100-mg. anthisan tablet. Following the injection I experienced no immediate reaction, and as anthisan always makes me sleepy I rested. About 20 minutes after receiving the injection I had a sudden flushing of the face, marked tachycardia, a feeling of impending doom, and an urgent desire to evacuate my bowels, passing a large quantity of watery stool. After an hour I felt sufficiently well to carry on with my work.

In view of the manufacturer's statement that only insignificant traces of antibiotics may still remain in the vaccine, I put down my "allergic" reaction following the injection to a state of "neurosis" occasioned by my experiences with the penicillin in 1956 and the achromycin. But, having read Dr. Fowden's article, I have decided not to have the second injection. It is evident that persons allergic to penicillin may suffer severe reactions from poliomyelitis vaccine even when it contains "insignificant traces" of antibiotics.—I am, etc.,

Las Palmas, Canary Islands. STANLEY S. PAVILLARD.

SIR,—The memorandum by Dr. A. Fowden in your issue of October 4 (p. 835) describing an allergic reaction following an injection of British poliomyelitis vaccine, and your annotation on this subject in the same issue (p. 843), prompt me to report the following case which occurred recently.

Vaccination against poliomyelitis was requested at a local authority clinic for a child aged 4 with a history of infantile eczema which still occasionally gave trouble. There was, in addition, the history that, following three or four doses of an oral preparation of penicillin given about 12 months previously for a tonsillar infection, the child developed, about 24 hours after the first dose, a severe generalized rash, which the mother described as nettlerash. The penicillin was stopped and the rash cleared up after about three days without any specific treatment. No family history is available, as the child is adopted.

The vaccine used was a Salk vaccine, prepared in America, during manufacture of which penicillin and dihydrostreptomycin are stated to be added in amounts not exceeding 200 units and 200 micrograms respectively per ml. The final vaccine is said to have little or no penicillin activity, but the dihydrostreptomycin is stated not to be significantly affected by the manufacturing process. It is further claimed in the manufacturers' descriptive leaflet that individuals with known penicillin sensitivity have been immunized without ill effect. However, the manufacturers suggest that highly allergic individuals should be tested cautiously with very small initial doses of vaccine given intradermally, and in view of the history it was decided to proceed along these lines in the case under discussion. Accordingly, a dose of 0.1 ml. of vaccine was injected intradermally, and, as no ill effect or local reaction followed this, 0.5 ml. was injected subcutaneously one week later. The child was brought again to the clinic after an interval of three weeks, and the mother reported that 48 hours after the second injection the child developed an extensive rash consisting of weals like nettlerash and similar to that following the oral penicillin the previous year. The reaction on this occasion also included severe vomiting, and this persisted for four or five days, while the rash lasted about three days. The child's family doctor confirmed the urticarial nature of the rash and absence of precipitating factors other than the poliomyelitis vaccine. The child remained apyrexial throughout. As on the first occasion, the reaction cleared up without treatment; an antihistamine preparation prescribed by the family doctor was not administered by the mother.

The resemblance of this case to that of Dr. Fowden and to those mentioned in your annotation is evident, and, despite the manufacturers' claim to have virtually eliminated penicillin from the final vaccine, it seems likely that sufficient remained to bring about an allergic response in a child whose high sensitivity to this antibiotic had already been demonstrated by her reaction to its oral administration, although one cannot eliminate the possibility that the streptomycin was the cause.—I am, etc.,

Bromhills, Staffs. C. BURNS.

SIR,—I was interested to read the case report by Dr. A. Fowden and your annotation on reactions to penicillin in poliomyelitis vaccine (*Journal*, October 4, pp. 835 and 843). The development of the clinical picture in Dr. Fowden's case leaves little doubt that headache was the first symptom of penicillin allergy. Contrary to the usual belief, headache is a common manifestation of sensitivity reactions. In a recent large series of my own, it was present in 24% of patients allergic to antituberculous drugs. With regard to your annotation, it is well recognized that antihistamines have no general effect in these cases and desensitization is rarely possible under their cover alone.[1] On the other hand, I have found corticotrophin very valuable in these reactions,[2] both as a suppressing and a desensitizing agent, especially if given round the clock. Zimmerman[3] does not state the dosage of corticotrophin in his series, nor had he given corticotrophin or other steroids to all his six patients. Since, as he states, polio vaccine contains monkey protein, horse serum, formaldehyde preservatives, and other antibiotics—all potential causes of allergic reactions—I suggest that all such cases should be treated adequately with corticotrophin—i.e., at least 40 mg. or more to be given daily in divided dosage. Many of these so-called resistant patients should respond well on an adequate dosage of corticotrophin. As there is always a dangerous possibility of a later development of anaphylactic reaction, every allergic individual must be desensitized. Penicillinase might relieve the symptoms of penicillin allergy, but surely this should not be the ultimate goal.—I am, etc.,

Harts Hospital, Woodford Green, Essex. S. K. GUPTA.

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Post-parotidectomy Gustatory Sweating

SIR,—We were very interested to read the observations of Messrs. D. H. Glaister, J. R. Hearnshaw, P. F. Heffron, A. W. Peck, and Mr. D. H. Patey (*Journal*, October 18, p. 942) on the mechanism of post-parotidectomy gustatory sweating. However, in dealing with the possible causes of this condition they failed to consider the phenomenon of collateral sprouting, which provides at least as likely an explanation as any of those they mentioned. This type of nerve regeneration has been shown by direct experimental methods to result in the appearance of new and paradoxical associations of normally unrelated nervous pathways.[1 2]

Until recently it was generally supposed that, if a nerve is interrupted by injury or disease, no restitution of function can occur until new fibres grow out from the divided central stump to reach denervated structures. However, the nervous system possesses power additional to that normally understood by regeneration. In this phenomenon known as collateral sprouting, remaining intact nerve fibres, in response to a stimulus from adjacent degenerating fibres, give off side-branches or sprouts. These grow into near-by tracks left by the degenerating axons and are thereby guided to denervated endings.

This phenomenon of collateral sprouting is extraordinarily efficient in the autonomic nervous system. For example, in the cat, preganglionic denervation of the superior cervical ganglion was performed by resection of 3 cm. of the cervical sympathetic trunk. Several months later, histological examination and electrical stimulation of the cervical trunk showed that, whilst classical regeneration across the gap had not taken place, sprouting had occurred from efferent vagal fibres in the region of the nodose ganglion. As a result, the superior cervical ganglion had become partly re-innervated by efferent vagal fibres, thus producing a bizarre situation in which the pupil and nictitating membrane became functionally linked with gastric and vascular reflexes.[2]

In the case of gustatory sweating following injury or disease of the parotid gland, parasympathetic secretomotor fibres in the peripheral distribution of the auriculotemporal nerve will sprout and may acquire additional functional connexions with sweat glands, as we previously suggested.[2] Conversely, a cholinergic sympathetic fibre may come to innervate both sweat glands and parotid tissue. In comparable circumstances to these, we have shown that exaggerated responses occur, and are due to the summation of the effects of partial re-innervation and persisting hypersensitivity. It was therefore with particular interest that we noted that Glaister *et al.* had found that, in 8 out of 10 patients with gustatory sweating, the sweat glands showed an increased sensitivity to acetylcholine on the affected side.

The practical importance of considering collateral sprouting as a mechanism becomes evident in the recurrence of gustatory sweating after avulsion of the auriculotemporal nerve. Whether or not re-innervation is due to classical regeneration across the gap can be tested directly. If, however, it is due to collateral sprouting, then the essential therapeutic attack would be not to resect a greater length of nerve but to find the central level at which division of the nervous pathway eliminates from the affected area the supply of parent fibres from which appropriate sprouting can arise.—We are, etc.,

Department of Surgery, University of Aberdeen. J. G. MURRAY.

Department of Pharmacology, Royal College of Surgeons of England. J. W. THOMPSON.

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Sex Education for Students

SIR,—In the *Journal* of October 25 (p. 1029) you published an annotation on sex education for students. Some of the remarks in this are open to severe criticism and show little appreciation of the problems involved in the maturation of the individual or of the place of these problems in clinical medicine. The annotation states that "some students are scarcely sufficiently mature and stable to accept the emotional effort entailed in studying a subject of this kind." If this is true, how can such a person be fit to practise as a doctor? Surely the time to find out if this is the case is before qualification and not when it may well be too late for the doctor to make an adequate adjustment. The statement implies that maturity and understanding of marital problems is something picked up as the years roll by. This Victorian attitude would hardly be acceptable to modern psychiatry, and to ignore the problem amongst undergraduates is evading the responsibility which all teachers concerned should feel.

The second statement—"Not only is the student unaware of the emotional problems involved in marriage but often ignorant of his own ideas, fantasies, and prejudices about the sexual and marital relationship"—shows a considerable ignorance of medical students. One cannot lump medical students together as "the student," nor can one generalize in this way. Surely an average, intelligent medical student of 23 or 24 cannot spend three years among the patients of a teaching hospital and remain unaware of emotional problems of marriage. So much of clinical medicine is, in some way or another, bound up with family life and marital relations. So many illnesses are functional in nature, and so often an organic disease has a profound psychological overlay. How can one justifiably divorce one of the major aetiological factors of modern medicine from clinical teaching?

Your annotation goes on to speak of a voluntary method of teaching, and says that "the drawback to this is the danger that those struggling with their own emotional problems are particularly attracted to the subject, and the resulting strain may precipitate a breakdown." That this is theoretically possible is no doubt true, but if we are to have remarks of this kind in the leading British medical journal then let them be backed up with facts and figures.

It is to be regretted that your annotation obscures the basic issues. Medical students need to have their own problems solved and to receive a good grounding in normal family life and the place of the family in society. If the student is helped with these, the psychiatric and gynaecological problems which occur can easily be dealt with in the proper place.—I am, etc.,

London, W.C.1. EDWARD J. R. ROSSITER, Education Officer, British Medical Students' Association.

Foetal Phonocardiography

SIR,—I note that Dr. C. N. Smyth and Miss Jennifer L. Farrow state in their paper in the *Journal* of October 25 (p. 1005) that they have paid little attention to the acoustic quality of the foetal heart sounds, and have limited their studies principally to time relationships. This is understandable in their case, as they used a moving-iron microphone. Sensitivity and robustness are not of themselves sufficient, especially now that first-class high-sensitivity pickups have been introduced.

I note with surprise that they found it necessary to use a loudspeaker which had to be situated in a different room to the microphone to prevent "howling round" or acoustic instability. Still, they found it fairly essential to have some form of acoustic heart signal in the same room as the patient, but they did this by the inelegant method of converting the foetal heart sounds into—quoting their own words—"plops," which would be heard by the pregnant woman. The foetal heart sounds can be demonstrated in the same room as the patient by the use of a proper pick-up and close-fitting, suitable headphones, skilfully used. Acoustic feed-back is prevented as there is no direct acoustic path between the headphones and the proper pickup. This methods permits the auscultator or auscultators to hear the foetal heart sounds at the same time as they are being recorded, without the patient hearing them.—I am, etc.,

West Glamorgan Health Division, Swansea. G. E. DONOVAN.

Ergometrine with Hyaluronidase

SIR,—I was interested to see Dr. A. H. Labrum's letter (*Journal*, October 4, p. 857) regarding the intramuscular injection of ergometrine with hyaluronidase. He suggests that the addition of hyaluronidase both enhances and speeds the action of ergometrine but that the effect diminishes as the dose of ergometrine increases. The proof may not be adequate, but if his contentions are correct then any advantage of the hyaluronidase method could be achieved by merely increasing the dose of ergometrine alone; though I hardly think Dr. Labrum is suggesting this.

The widely varying figures quoted by Dr. Labrum well illustrate the difficulty of interpreting and comparing the results of different clinical trials; clearly, the incidence of post-partum haemorrhage in a particular series is influenced by other factors besides the type of ergometrine technique employed. Kimbell's results[1] were certainly excellent; but I am not surprised that good results have been reported giving ergometrine and hyaluronidase at the end of the second stage of labour. On the other hand I feel that the plain ergometrine injection is capable of good results too. Comparatively few figures are available, but they are not unimpressive. Thus, I might point out that Daley's[2] post-partum haemorrhage rate of 9.2% with the plain ergometrine technique (quoted by Dr. Labrum) represented a great improvement on an incidence of 15.7% in the control group, while in primigravidae only the

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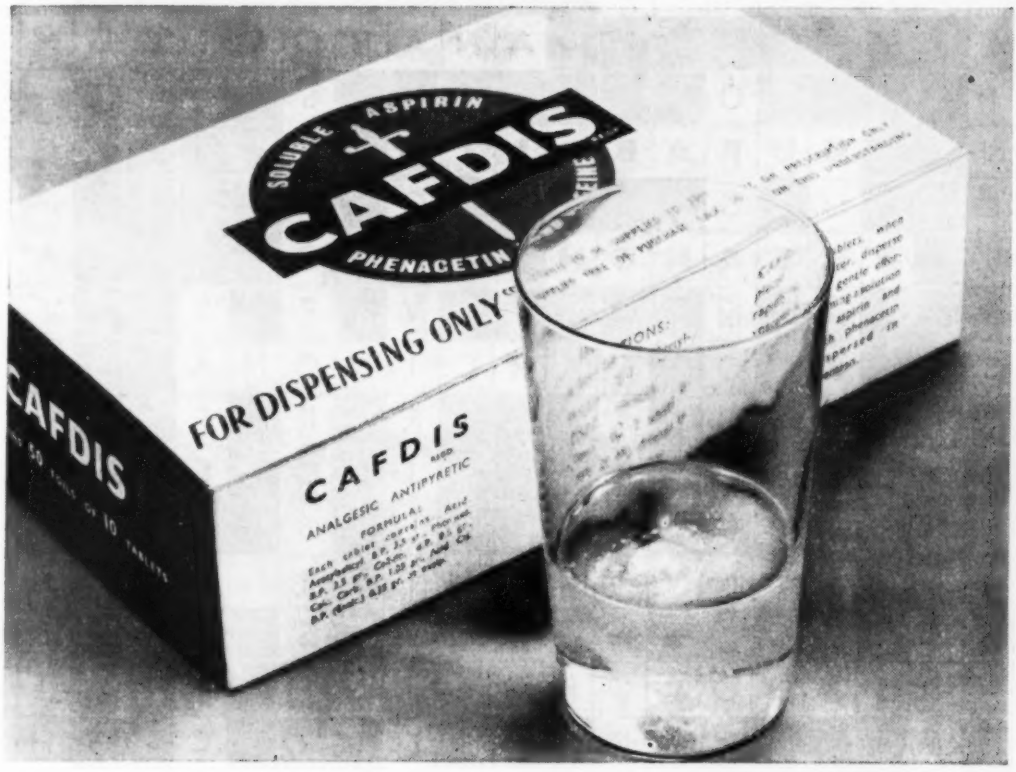

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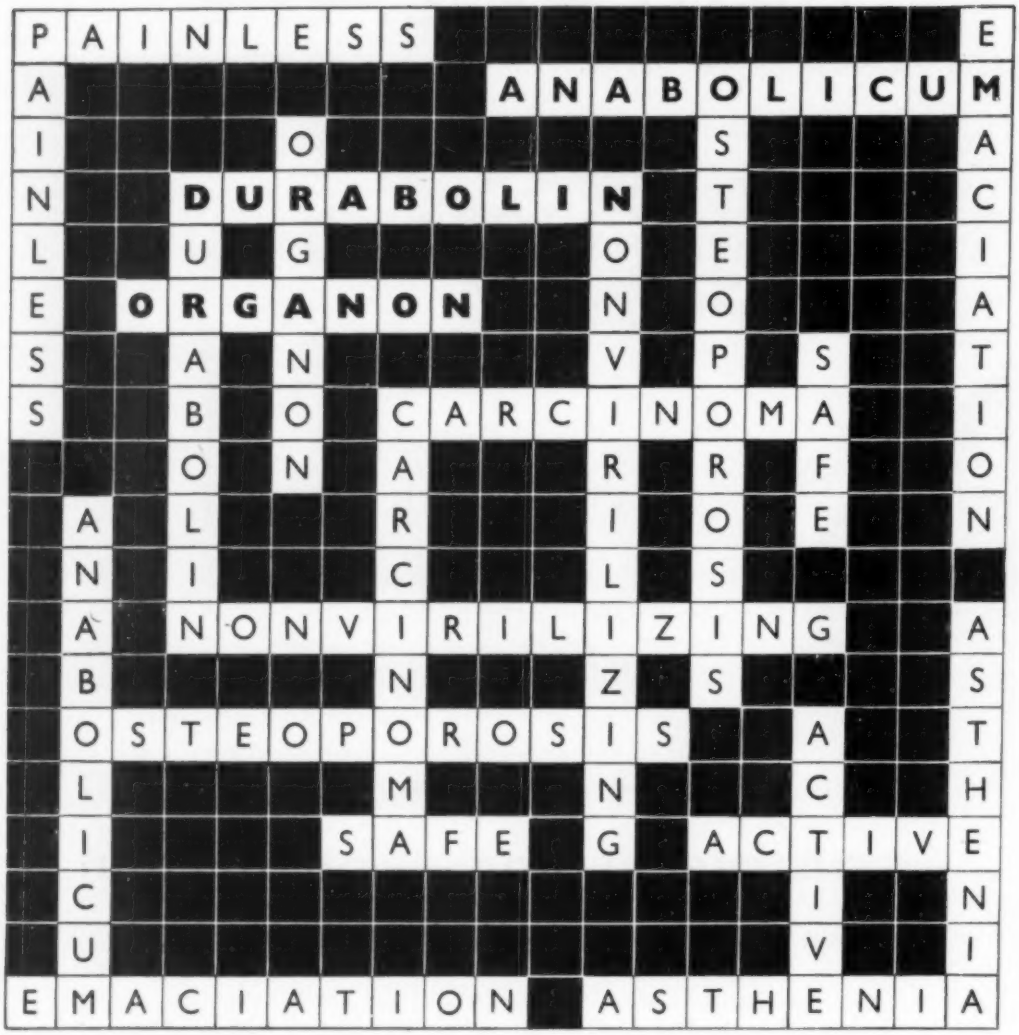

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incidence of haemorrhage dropped from 13.2% to 5.2%. Such results scarcely justify the implication that to omit hyaluronidase from the intramuscular injection of ergometrine is to court disaster.

As I have already pointed out (*Journal*, September 13, p. 692), Mr. W. J. Garrett and I based our opinion of the intramuscular injection of ergometrine with hyaluronidase (*Journal*, July 19, p. 138) on objective measurements of its speed of action compared with ergometrine alone. Our observation showed that while hyaluronidase unquestionably accelerated the action of intramuscular ergometrine the latent period was reduced only by one-third. We readily acknowledged the value of the method as a "stop-gap" procedure; but, having regard to the greater difficulty in making the injection (Dutton[3] reports a 19.5% failure rate) and the cost, it seemed to us that there was some doubt as to its superiority over the plain ergometrine technique as a routine method.—I am, etc.,

The Radcliffe Infirmary, Oxford. MOSTYN P. EMBREY.

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2 Daley, D., *J. Obstet. Gynaec. Brit. Emp.*, 1951, **58**, 388.
3 Dutton, W. A. W., ibid., 1958, **65**, 315.

SIR,—When Dr. J. N. Gale (*Journal*, October 25, p. 1044) advocates giving ergometrine after delivery of the placenta to avoid its retention he is bowing to tradition, not to the needs of present-day practice. The object of giving ergometrine with the anterior shoulder is to prevent post-partum haemorrhage, a condition which causes morbidity and mortality. In the recent Ministry of Health Report Number 97 on Confidential Enquiries into Maternal Deaths in England and Wales 1952–1954 (obtainable from Her Majesty's Stationery Office, price 3s. 6d. net) there were 113 deaths from post-partum haemorrhage, and "almost all the deaths in this group were entirely due to haemorrhage or a combination of shock and haemorrhage." Manual removal of the placenta in a fit patient is without risk; it is the results of manual removal in the exsanguinated patient which formerly brought the procedure into disrepute. It is a proved fact that the longer the third stage of labour the greater is the danger of post-partum haemorrhage. A contracted uterus does not bleed even with the placenta *in situ* and a contracted uterus cannot be inverted by cord traction. For dissertations on the modern management of the third stage of labour, I would refer Dr. Gale to the papers of Norman Kimbell[1 2] and F. C. R. Picton.[3]—I am, etc.,

Obstetric Hospital, University College Hospital, London, W.C.1. W. G. MACGREGOR.

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3 Picton, F. C. R., *J. Obstet. Gynaec. Brit. Emp.*, 1951, **58**, 764.

Premonition of Death

SIR,—I hope we shall not be losing our sense of perspective on premonition of death. This symptom is more apt to occur when there is some genuine cause for it, whether it be known or unknown to the doctor, and hence is not lightly disregarded. Furthermore it is readily remembered when it proves an accurate forecast. Before we attach any greater importance to it than we do already we should remember that, unless a valid comparison is made with cases in which this premonition has proved false (by no means an easy thing to do), we should do well not to allow ourselves to wander on to the borders of spiritualism.

I have under my care an old lady of 86 who for the past eight years has at intervals of three to four months decided that her end was nigh and asked that her offspring be brought to her that she might bid them farewell. Since they visit her daily I have always felt constrained to treat her seriously every time it happens. One of these days she may be right—but so far she has merely been a cause of alarm to her relatives and anxiety to me.—I am, etc.,

London, W.9. A. LEWIS.

Buzzers for Bed-wetters

SIR,—A clinic for the treatment of enuresis was started four years ago by the public health department of Croydon. During the past two years electrical anuretic machines have been loaned to those cases that have resisted simpler forms of treatment.[1] Up to date 45 children have used these machines and there have been no failures. (There have been two relapses following domestic upheaval after several months' complete dryness.) The average duration of treatment is two months.

The initial cost of the machines is five guineas, and, allowing for minor repairs and replacement of batteries, one machine will last for years of continuous use. The first machine bought for the clinic is two years old and still in service. The cost of one brand of pituitary snuff is 22s. 6d. for 25 capsules and insufflator. I believe that its use is quite well known, as several children attending the clinic have previously been treated with it unsuccessfully. In my experience the electric "buzzer" is a cheaper form of treatment than the use of pituitary snuff for several months as recommended by Dr. Clifford Allen (*Journal*, September 27, p. 799).—I am, etc.,

Public Health Department, Croydon. MARGARET WHITE.

REFERENCE
1 White, M., *Med. Offr.*, 1957, **98**, 125.

Infectious Mononucleosis

SIR,—In your leading article (*Journal*, October 11, p. 899) reference is made to the possible role of *Listeria monocytogenes* and of a virus in the causation of infectious mononucleosis. I would like to add that an organism intermediate between the Rickettsiae and the larger viruses was isolated in three cases of infectious mononucleosis in Japan in the years 1953, 1954, and 1955 (*Rickettsia sennetsu Misao-Kobayashi*). The experimental disease produced in human volunteers by the hypodermic injection of emulsions prepared from lymph nodes and spleens of mice experimentally infected with *R. sennetsu* was in every respect a typical glandular fever.[1]

Much remains to be learned about the aetiology of infectious mononucleosis. It must, however, be emphasized that at our present state of knowledge—or lack of knowledge—of the causative agent(s) patients exhibiting the typical haematological picture should be considered as cases of infectious mononucleosis in spite of a negative Paul–Bunnell reaction. Tests for toxoplasma antibodies might, in a very small proportion of such cases, reveal the presence of toxoplasmosis, but the number of toxoplasma-positive cases will be infinitesimal.—I am, etc.,

City General Hospital, Sheffield. S. VARADI.

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Prevention of Lung Cancer

SIR,—Mr. Leslie J. Temple has a peculiar way of bringing home to the public the hazards of excessive cigarette smoking (*Journal*, October 4, p. 858). He believes that holding inquests in cases of death from carcinoma of the bronchus would lead to moderation in cigarette smoking.

I saw this week a young girl in my surgery who is expecting her baby next month. She told me she is smoking 30–40 cigarettes a day and makes them herself, using strong tobacco. I told her that she was smoking too many cigarettes and asked her why. She replied, "I have not seen my husband for four days and I don't know where he is. I am worried and that is why I am smoking heavily." I believe this is the answer why some people smoke excessively—worries, tension, and the tempo of modern life and civilization.

Inquests are held every day in cases of road fatalities, but has that led to reduction in road accidents? What we need is not more inquests but a more and more psychiatric approach as to why people smoke excessively.—I am, etc.,

Liverpool, 18. H. J. PRATAP.

Obituary

Sir JOHN MEGAW, K.C.I.E., D.Sc., M.B., B.Ch.

Sir John Megaw, a former Director-General of the Indian Medical Service, died at his home at Hawkhurst, Kent, on October 24 in his 85th year. He was known throughout the world as an authority on the rickettsioses, as a zealous advocate of population control by family planning, as a pioneer of air-conditioning in the tropics, and as the *fidus Achates* of Sir Leonard Rogers, who, now in his nineties, survives him.

Born on February 8, 1874, in Ballyboyland, not far from Ballymoney in Co. Antrim, John Wallace Dick Megaw was educated at the Belfast Royal Academical Institution and at Queen's College, Belfast, and graduated M.B., B.Ch., B.A.O., with first-class honours, at the Royal University of Ireland in 1899. He had a brilliant student career, being Dunville student at Queen's and winning several scholarships and exhibitions, but after graduation he never took any other degree, being doubtful of the usefulness of time spent in acquiring "higher qualifications." His own university honoured him by conferring on him the D.Sc. (hon. causa) in 1934. He entered the Indian Medical Service in 1900, and after a brief spell of military duty, during which he saw active service in China, he was transferred to civil employment in Bengal in 1903. During the ensuing ten years he spent much of his time in the varied employment undertaken by district medical officers in India. When resident medical officer in the Medical College Hospital, Calcutta, he helped Leonard Rogers with the clinical side of his cholera researches—the commencement of a life-long bond. Developing a special interest in pathology and bacteriology, Megaw underwent advanced training in pathology and bacteriology when on furlough and study leave. In 1914 he was appointed professor of pathology at Lucknow University—a post which he later combined with that of principal. While in Lucknow he undertook and directed research on beriberi and dengue and sandfly fevers, and, as a result of a personal illness, on non-epidemic typhus fevers, a subject in which he took the liveliest interest throughout the rest of his life.

Founded by the drive and energy of Sir Leonard Rogers, through whose persuasive powers the necessary money was raised, the new Calcutta School of Tropical Medicine and Hygiene was fortunate in its first director, John Megaw, who took it over in 1931. He surrounded himself with an outstanding group of research workers and teachers: driving his colleagues hard, he encouraged them by his own example. During his term of office the output of research work of real worth was very striking. He commenced then his studies on the effects of heat and humidity on efficiency and did pioneer work on air-conditioning in the tropics. From 1921 to 1928, in his spare time, he edited the *Indian Medical Gazette*, and from 1928 to 1930 he was president of the South Indian and Madras Branch of the B.M.A.

Appointed C.I.E. in 1926, he became Inspector-General of Civil Hospitals in the Punjab in 1928, but a few months later he was promoted Surgeon-General with the Government of Madras. While in Madras he made his famous observation: "There is no quinine-resistant malaria—there is much dispenser-resistant malaria." With Hawley he devised improved simple methods for estimating quinine in liquids, and many petty pilferers were dismayed.

In 1930 Megaw became Director-General of the I.M.S., and on his retirement in 1933 he was promoted K.C.I.E. During his tenure of that high office his statesmanlike qualities became apparent to all who met him or read his writings. The question of over-population of India was constantly in his thoughts; he strove unceasingly for the improvement of medical education—especially in the field of hygiene—and the need for training Indians to "take over" was keenly appreciated by him. On leaving India he succeeded his old friend Sir Leonard Rogers—with whom he had written a successful book entitled *Tropical Medicine*—as medical adviser to the Secretary of State for India and president of the India Office Medical Board. While in London he became a part-time lecturer at the School of Tropical Medicine and Hygiene. He gave up office in 1939 on reaching the age limit. He was Honorary Physician to the King from 1930 to 1934.

After retirement Megaw devoted his days to practical scientific farming in Kent, working with both hand and brain to make a success of his estate. His evenings and nights were devoted to his literary labours for the *Tropical Diseases Bulletin* and to the development of a new international language which, he hoped, might make the task of future abstracters of foreign literature less bothersome. He remained to the end modest and simple, but critical of loose arguments and mental woolliness. He was intensely interested in every branch of medical science, and on his deathbed suggested better ways of inserting the muscles of the lower limb so that a fallen invalid could get into bed more quickly before his nurse could discover that he had crept out.

In 1912 he married Helen Esmée Ward, who survives him. There were no children.

Dr. CHARLES WILCOCKS writes: Sir John Megaw did not end his association with research in tropical medicine when he retired from the Indian Medical Service, but his later interest was literary, and it was in this field that he made a very notable reputation after retirement. For several years he served on the honorary managing committee of the Bureau of Hygiene and Tropical Diseases, and from 1941 onwards he undertook to review papers on the rickettsial diseases and other fevers for the *Tropical Diseases Bulletin* and the *Bulletin of War Medicine*. His interest in these diseases had been stimulated in India by an attack of what he recognized as tick typhus, and he had built up a system of classification by vector—louse, flea, tick, mite—which certainly simplified and clarified our conception of these diseases, and which, he maintained, fitted in remarkably well with the results of the specific rickettsia-agglutination test and the complement-fixation test. He preferred this classification to one based on the Weil–Felix test, useful though that test is, because with the Weil–Felix test the louse-borne and the flea-borne diseases cannot be distinguished, and in the tick-borne group the reactions are highly irregular.

The rickettsial diseases became very important during the second world war, when epidemics of louse typhus swept North Africa and Italy, scrub typhus was a major complication of the Far Eastern campaigns, and Q fever was for a time something of an enigma round the Mediterranean. Megaw took very seriously the work of reviewing papers on these subjects, written in many languages (none of which seemed to give him any trouble), and his cool and critical scrutiny of these papers, and his faculty of giving in few words the essence of their information, was widely appreciated throughout the world. His comments were quoted and discussed by the most eminent of research workers, and his opinions were constantly sought. It was always a pleasure to receive his manuscript. His facts were correct and there were no wasted words, and his language was clear and definite and characteristic. His writing was always

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interesting, and it had a certain graceful quality which came, I think, as an unconscious by-product of the clarity of his thought. *Nullum quod tetigit non ornavit.*

Megaw kept up to date with medicine, and was as familiar with the work on dengue and the related fevers, and on plague, as he was with typhus. When we asked him to do something outside his usual line the reply would always be, "Send it along and I'll see what I can do," and the result would be superb. He was a statesman, as could be seen from his published appreciation of the Bhore Report on medical services for India, published in 1946, and he was generous. We have lost a great man.

IVOR J. DAVIES, C.B.E., M.D., F.R.C.P.

Dr. Ivor Davies, consulting physician to the Cardiff Royal Infirmary and the Ministry of Pensions hospital at Rookwood, Cardiff, died at his home at Aberystwyth a few days after his 78th birthday.

Ivor Jones Davies was born on October 22, 1880. Beginning his medical studies at University College, Cardiff, where he won several scholarships, he went on to St. Bartholomew's Hospital, graduating M.B., B.S. of London University in 1906. After holding a number of resident appointments at the Royal Free Hospital, including that of house-surgeon to Sir James Berry, he took the M.R.C.P. and proceeded to the M.D. in 1911. Returning to practice in Cardiff, he soon became established as a consulting physician, though his work was interrupted by service in the first world war. He was a pioneer in pulmonary diseases caused by dust, though essentially a general physician, and his contribution to the literature included a paper on goitre in South Wales, a subject which had particularly interested him since his association with Sir James Berry. One of his earliest papers, published in this *Journal*, was on the subject of carbon monoxide poisoning after an explosion in a coal-mine. Dr. Davies was appointed first assistant to the first professor of medicine (Dr. A. M. Kennedy) in the newly established medical unit at the Cardiff Royal Infirmary. In 1922 he became a full physician there, and three years later he was elected F.R.C.P. When the B.M.A. held its Annual Meeting in Cardiff in 1928 he served as a vice-president of the Section of Medicine. For his work at the Ministry of Pensions hospital at Rookwood he was appointed C.B.E. in 1953.

L. R. writes: Dr. Ivor Davies had recently attended the meeting in Cardiff of the Fellows and Members of the Royal College of Surgeons, where he had met many old friends and had been in good spirits. He was always a vivid, cheerful, kindly character with a keen sense of humour which made him one of the best of raconteurs. A lifelong supporter of the best interests of the Cardiff Medical School and of his profession, he paid frequent visits to London to keep in touch with the Royal College of Physicians, to which he became an examiner, and with his former associates at St. Bartholomew's. His practice soon became one of the busiest in South Wales, for it was generally realized that he was not only an able physician but one who had a lovable character which inspired confidence in both patients and practitioners. Perhaps his outstanding contribution to medicine in Wales was his staunch loyalty to the young medical school during its formative years; he frequently had to play an unpopular part at a time when birth pangs were sometimes acute through the obstruction of established custom. He was a devout Churchman, a Rotarian, and a keen student of both Welsh and medical history. In 1943 he retired from the Cardiff Royal Infirmary and six years later went to live in Aberystwyth, his wife's home town, but from time to time he visited Cardiff to see his old friends and his patients at the Ministry of Pensions hospital. He leaves a widow and two daughters, to whom we extend our sympathy.

J. V. LANDOR, M.D., M.R.C.P., D.P.H. D.T.M.&H.

Dr. J. V. Landor, who spent the greater part of his professional life in the Colonial Medical Service, died at the Royal North Shore Hospital, Sydney, New South Wales, on September 12.

Joseph Victor Landor (formerly Landau) was born in 1897. He received his medical training at St. Bartholomew's Hospital and graduated M.B., B.S. from London University in 1920, taking the London Conjoint diploma in the same year. Proceeding to the M.D. in state medicine in 1925, he took the D.P.H. of the English Royal Colleges in the following year and the D.T.M.&H. in 1927. He was elected M.R.C.P. in 1932. After holding the appointment of house-surgeon at the Royal Northern Hospital, Holloway Road, London, he entered the Colonial Medical Service in 1927 and served until 1946. He was chairman of the Southern Division of the Malaya Branch of the British Medical Association in 1935–6. In 1947 he went to Australia and became assistant chief medical referee to the Government Insurance Office in Sydney, New South Wales. He leaves a widow.

A former colleague writes: In the Colonial Medical Service Dr. J. V. Landor worked as a medical officer in Singapore, Jahore, and Penang before being promoted to the post of physician to the General Hospital, Singapore, where he remained until his retirement. While in Jahore his duties included the medical care of prisoners in the gaol, among whom he observed symptoms of an ill-defined nutritional disorder. Working in collaboration with the medical officer of the Singapore gaol, where a similar condition occurred, the symptoms were described and the aetiology of them was studied. At the time of this work vitamin B was known to consist of the anti-beriberi factor B_1 and a heat-stable factor B_2. The "prison disease" was considered to be due to a deficiency in this latter part, and later, when riboflavine was discovered, it became evident that part of the syndrome that had been described resulted from lack of this vitamin. When the Japanese invaded Malaya Dr. Landor was interned in Singapore for three and a half years and was himself exposed to the dangers of the deficiency conditions he had helped to describe. During those years of internment he worked in the camp as dermatologist, and his special experience in dietetic disorders was put to good use in the service of his companions. Ariboflavinosis, pellagra, and other obscure skin conditions, probably nutritional in origin, became increasingly common as the years of confinement passed. The quiet skill and care with which he diagnosed and attempted with inadequate means to treat his patients was appreciated by all who were interned with him, and his work was a valuable contribution to the maintenance of the morale of the camp. He kept careful records of the dermatological lesions that he had seen, and as soon as he was released he published an account of his observations in the *British Journal of Dermatology* in 1948. After the war had ended he returned to his post of physician in Singapore, but, owing to ill-health, was soon forced to retire. He then settled in Australia, where he lived until his death.

C. M. OCKWELL, M.D., F.R.C.S., D.P.H.

Dr. C. M. Ockwell, who formerly practised in Dartford and was medical officer of health for Crayford, Kent, for over a quarter of a century, died at Guy's Hospital on October 17. He was 74 years of age.

Charles Melton Ockwell received his medical training at Guy's Hospital, qualifying M.R.C.S., L.R.C.P. in 1906. He was admitted to the F.R.C.S. in 1919, took the Cambridge D.P.H. in 1920, graduated M.B., B.S. of London in 1930, and proceeded to the M.D. in 1934. After qualification he was in general practice at Burgh, Lincolnshire, for a few

years before joining Dr. M. W. Renton in partnership at Dartford in 1914. During the first world war he was a surgeon at a base hospital at Fécamp for a year, and thenceforward until the end of the war ophthalmic specialist at the Royal Herbert Hospital, Woolwich, and at Paddington military hospital. After the war he became interested in preventive medicine. Appointed medical officer of health for Crayford in 1921, his duties were extended a few years later to include the Swanscombe urban and Dartford rural districts. Later he was appointed venereologist under the Kent County Council. Ultimately he became a full-time medical officer of health. In Crayford he developed the maternity and child welfare services, and was one of the first medical officers to offer diphtheria immunization to the children in his area. When the National Health Service came into being in 1948 he was graded consultant dermatologist and venereologist. A member of the British Medical Association for 40 years, he was chairman of the Dartford Division in 1924–5 and again in 1934-5, and president of the Kent Branch in 1937–8. He was also a member of the Library Subcommittee at Headquarters from 1933 to 1943. He resigned his appointment of medical officer of health for Crayford in 1947, and retired almost completely four years later. He kept up his interest in medicine to the end, however, and since his official retirement had acted as locum tenent on numerous occasions. In 1951 he married Miss Kathleen Keirle and moved to a new house on the Pilgrim's Way at Kemsing. His death has caused keen distress among his many friends and colleagues, for he was very popular and his reputation as a doctor was deservedly high.

RICHARD COLBY, M.R.C.S., L.R.C.P.

Dr. Richard Colby, who had been in general practice at West Wickham, Kent, for the last 14 years, died at Farnborough Hospital on October 2. He was 47 years of age.

Richard Colby (formerly Kobylinski) was born in Berlin on February 24, 1911, and studied medicine there and at Heidelberg. He was within three months of qualification in 1933 when he was forced to leave Germany on account of Nazi oppression. He came to England, where he had to begin his studies (including those for matriculation) all over again. After receiving his clinical training at St. Bartholomew's Hospital he qualified M.R.C.S., L.R.C.P. in 1940. He then held appointments at Warlingham Park Hospital, Poplar Hospital, and Mayday Hospital, Croydon, before entering general practice at West Wickham in 1944. He was chairman of the Bromley Division of the British Medical Association in 1955–6, and was a member of the Kent local medical committee and medical adviser to the Bromley branch of the Marriage Guidance Council.

K. B., a local colleague, writes: For the past ten years Dr. Richard Colby was associated with the work of the Bromley branch of the Marriage Guidance Council and was its special representative at the yearly and half-yearly conferences arranged by the London headquarters. It was because of his sympathy for all unhappy people that he tackled the work with tremendous enthusiasm and spent many hours both with the couples who came to him and in giving talks so that the work of the council became known. He will be greatly missed by his colleagues and patients.

M. S. writes: Twelve years ago I was invited by Richard Colby to join him in partnership in general practice in West Wickham and Hayes, Kent. During these years I grew to know his personality intimately and to admire his work. He was a man of great zest and enthusiasm for many extra-medical activities. Despite his knowledge that his vascular system was suspect, he spent many of his off-duty hours in working for such causes as refugee relief, the "Save the Children" Fund, the Marriage Guidance Council, and the personal problems of patients and friends. To him the protection and preservation of the welfare of children were of paramount importance, and he was willing to give of himself for such causes. His own family life was undoubtedly the most happy and united that I have ever met. He leaves a courageous widow, two sons, and a daughter. They will miss him, as shall I and my family, my other partner and his family, and all our patients.

E. C. BEDDOWS, O.B.E., *M.C.*, M.R.C.S., L.R.C.P.

Brigadier E. C. Beddows, who had had a distinguished career in the R.A.M.C., died at Gullane, East Lothian, on October 3. He was 72 years of age.

Edward Charles Beddows was born at Wolverhampton on April 27, 1886, and studied medicine at Birmingham, qualifying M.R.C.S., L.R.C.P. in 1911. After qualification he held house appointments at Birmingham General Hospital before entering the R.A.M.C. as a lieutenant in 1913. Serving in France throughout the first world war, he was awarded the Military Cross in 1915, and in the same year was mentioned in dispatches. Between the two world wars he served in India, Gibraltar, and Shanghai, as well as at home. By the time the second world war broke out in 1939 he had attained the rank of lieutenant-colonel, and was with the British Expeditionary Force in France soon after the war began. Later he took part in the landings in Italy and Sicily. Promoted colonel in 1940, he was assistant director of medical services at No. 6 Base Area in 1943–4; deputy director of medical services for the North Africa District in 1944–5; and assistant director of medical services for the Berlin District in 1945–6. He was wounded at Bari in 1943. He was appointed O.B.E. in 1944 for distinguished services in Italy, and an Officer of the Legion of Merit of the United States of America in 1947. When he retired in 1946 he was granted the honorary rank of brigadier. He leaves a widow.

Medical Notes in Parliament

NEW SESSION'S EMPHASIS ON SOCIAL REFORM

In the new session—possibly the last of the present Parliament—the legislative stage has been set to focus attention on social reform. The Queen's Speech, on October 28, set forth the objective—"It will be the special care of my Government to introduce measures to promote the social well-being of my people"—and some of the method. If the Bill to provide pensions related to earnings is likely to be the most controversial, that to give effect to many of the recommendations of the Royal Commission on Mental Health and to replace the existing law on mental health is likely to occupy the most time. The PRIME MINISTER has indicated that it will be a "large" Bill; and the leader of the Opposition has expressed the hope that there will not be any great controversy about it.

Financing Mental Care

That there will be controversy about the financing of the new arrangements, however, seems certain. In the opening debates of the session two Opposition speakers, Mr. JAMES GRIFFITHS, the deputy leader, and Mr. ARTHUR BLENKINSOP, a former Parliamentary Secretary at the Ministry of Health, have voiced their concern at the likely effect of the block grant system of Exchequer aid on local authorities' resources for this purpose. Mr. Griffiths, with this reservation, promised constructive help and co-operation with the Bill when it comes to the House early next year. But later on the same day (October 29) Mr. Blenkinsop adopted a much sharper approach. To him, the Government were making an "empty promise" unless they produced a better

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statement of their intentions about finance than any so far given. The Royal Commission, he said, had made clear their own view that their recommendations could not be carried out effectively unless additional funds were available to enable local authorities to establish community care for the large numbers who ought not to be in mental hospitals and institutions. Some suspected, from what they knew of the discussions that had taken place, that the financial provision would not be present; and they believed that the introduction of the block grant system had destroyed the hope of effective progress in mental health and the care of the aged.

Factories Acts

The promise of legislation to amend and strengthen the Factories Acts, while welcomed, has also revived the Labour Party's grievance about the Government's failure to do anything about the the Gowers Report and so improve the conditions of shop and office workers.

Prison Reform

The increase in crime also received mention in the Speech. "My Government view [it] with gravity. In the light of the most up-to-date knowledge and research they will seek to improve the penal system and to make methods of dealing with offenders more effective." This is a subject on which the HOME SECRETARY has more than once indicated that he proposes to make haste slowly, in order to ensure that the changes shall be soundly based. The first lines of advance are to be drawn—probably in a White Paper, or some similar document—which Mr. Butler will present in a month or two, giving a full picture of what he has in mind. Thereafter there will be a process of testing public opinion, and obtaining the authority and guidance of those engaged in the administration of justice. Early legislation would not be advisable, but some would eventually be necessary.

This emerged from a debate on the subject to which the Commons devoted their time on October 31. The broad indications Mr. BUTLER gave point to an endeavour to secure more adequate treatment of the prisoner as an individual. For this, he said, there was needed a much more precise method of classification, and means to remove the jumbled grouping together of prisoners of all kinds, particularly the young with the old, so that they could be treated in suitable units. This entailed a considerable building programme. In dealing with young offenders the first rule was to preserve elasticity of judgment and diversity of treatment. He had put some ideas, which would in due course require legislation, to the Advisory Council on the Treatment of Offenders. The essential element was that, after sentence, more discretion should be left to the Prison Commissioners, Borstal governors, and others to handle young people as suited to their nature. This would mean for some a quicker period of training, education, redemption, and cure; and for the more obdurate the threat of longer detention. Figures Mr. Butler gave can be briefly summed up: Britain has half as much crime again as before the war. In spite of spectacular peaks and troughs in the statistics, the ground lost since 1939 had never been recovered. This was no sudden crisis, but a deep disorder in society. What was serious was the high rate of crime among young men between 16 and 21, for offences of all kinds. What was encouraging was that children under 14 had a better record than their predecessors, who as adults were now causing such anxiety. These severe problems of society could not be dealt with by the Government alone. They must enlist the co-operation of the whole country, the family, the churches, the schools. He refused to operate on insufficient information, but proposed to do a thorough and lasting job.

Prescription Charges

The speech in which Mr. HAROLD WILSON moved the Opposition amendment on November 3 criticizing the Government's economic policy, including "taking the lid off" measures against inflation, was barbed with a direct challenge to the Prime Minister on prescription charges. Two years ago, he recalled, when Mr. Macmillan was playing his "Mac the Knife" role as Chancellor of the Exchequer, he introduced a series of mean and vicious cuts of which the worst was the individual prescription charge. They were told at the time that this was essential for fighting inflation. Now the fight was off. The real enemy was recognized as a lack of spending power, not a surplus. To test the sincerity of the Prime Minister—that was how Mr. Wilson introduced his question—would the Government now remove the restrictions?

Rebuilding of Teaching Hospitals

Mr. A. BLENKINSOP (Newcastle upon Tyne, East, Lab.) asked the Minister of Health on November 3 what consultations took place with regional hospital boards regarding plans for the rebuilding of teaching hospitals. Mr. D. WALKER-SMITH.—I rely on boards of governors to consult the appropriate regional hospital boards, who are moreover represented by their own nominees on the boards of governors. Mr. BLENKINSOP, emphasizing that there should be full consultation to avoid wasteful decisions, asked him if he would look into the particular case of the North-east Metropolitan Board, to see if they were consulted about the changed plans for the new Charing Cross Hospital. Mr. WALKER-SMITH accepted the desirability of full consultation in all cases. If Mr. Blenkinsop had any question relating to a specific project he should put a question about it.

Medico-Legal

"INCURABLY OF UNSOUND MIND"

[FROM OUR LEGAL CORRESPONDENT]

By section 1 (1) of the Divorce (Insanity and Desertion) Act, 1958, a person is deemed to be under "care and treatment" for the purposes of section 1 (2) of the Matrimonial Causes Act, 1950, when receiving treatment for mental illness as a resident in hospital without certification. What was said to be the first case under the new section was heard before Mr. Commissioner Latey, Q.C., in the High Court recently, and judgment was given on October 28 (*The Times*, October 29).

The facts were that the parties were married in 1926, and had three children. The wife became a chronic alcoholic, and her condition became so bad in the colonial territory where her husband worked that in March, 1951, after being sent home to England, she was admitted to a mental hospital where she became a voluntary patient. She was transferred to Tone Vale Hospital, and there her condition improved so that in 1952 it was suggested that she might return home under supervision, but her husband, who had the children to look after, did not agree. Accordingly she remained in Tone Vale Hospital as an in-patient. The medical superintendent's evidence was that she was suffering from dementia and that no further improvement was possible, though he did not think she ought to be certified. It was therefore apparent that she had the volition either to stay in the hospital or to leave it.

Meanwhile after some years the husband began to live with his housekeeper, and, wishing to marry her, he petitioned for a dissolution of his marriage on the ground that his wife was incurably of unsound mind and had been under care and treatment continuously for the last five years for her condition.

In his judgment the Commissioner said that with the consent of counsel he had seen the specialist's report on the

wife which, as in all such cases, had been obtained by the Official Solicitor in his capacity of the wife's guardian *ad litem*. This was to the effect that the wife had become feeble-minded and childish, needed much nursing attention, and was in the light of present medical knowledge incurably insane. The Commissioner held therefore that the wife was incurably of unsound mind within the meaning of the section. He added that, in view of the recent policy of extending the range of voluntary patients and de-certifying certified patients, it might be that a large proportion of mental patients whether certified or voluntary would not come under the category of persons incurably of unsound mind within the Act, but each case must be considered on its merits.

The husband in this case got his decree, the Court exercising its discretion in his favour notwithstanding his adultery.

Vital Statistics

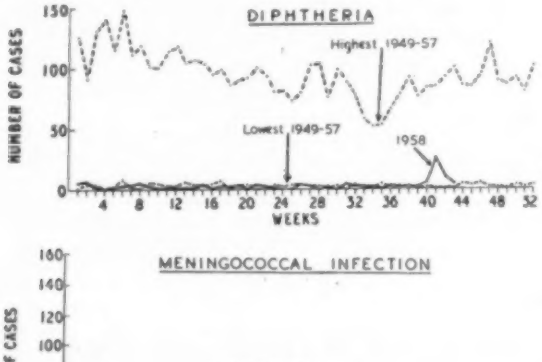
Industrial Accidents and Diseases

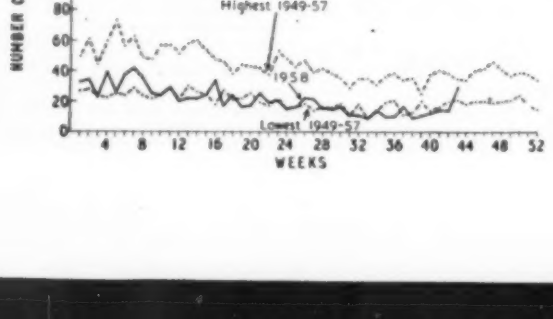
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in September was 104, compared with 55 in the previous month and 96 in September, 1957.

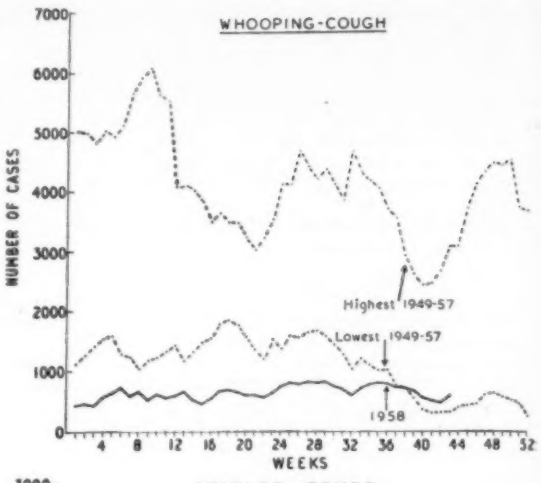
The numbers of cases of industrial diseases in the United Kingdom reported during September, 1958, were as follows: lead poisoning 4, aniline poisoning 3, compressed air illness 1, epitheliomatous ulceration 14, chrome ulceration 16; total 38. There were 2 deaths from epitheliomatous ulceration, 1 due to pitch and tar, and 1 to mineral oil.—*Ministry of Labour Gazette*, October, 1958.

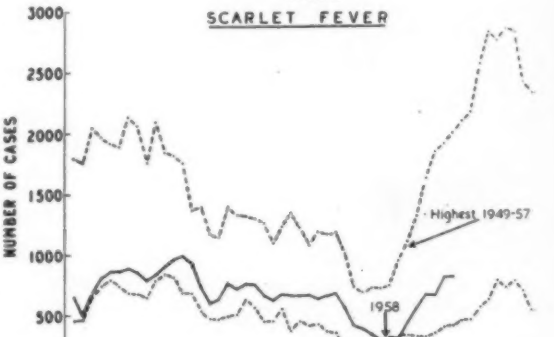
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus - - - - -, the figures for 1958 thus ———. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending October 25

The largest fluctuations in the notifications of infectious diseases in England and Wales during the week ending October 25 were increases of 493 for measles, from 3,739 to 4,232, 118 for whooping-cough, from 476 to 594, and decreases of 133 for dysentery, from 658 to 525, and 31 for food-poisoning, from 259 to 228.

The largest rises in the incidence of measles were 88 in Lancashire, from 456 to 544 (Liverpool C.B. 108); 63 in Derbyshire, from 78 to 141 (Chesterfield R.D. 46); 63 in Lincolnshire, from 102 to 165 (Gainsborough U.D. 72); the largest exception to an increasing trend was a fall of 59 in Buckinghamshire, from 88 to 29. The notifications of scarlet fever, 803, were 8 more than in the preceding week, and no large fluctuations were reported in the local returns. A small rise in the incidence of whooping-cough was reported from many areas, but the largest variation in trend was a fall of 24 in Lancashire, from 71 to 47. 4 cases of diphtheria were notified, 6 fewer than in the preceding week, and 3 of these cases were from the outbreak in London.

The notifications of acute poliomyelitis numbered 75, and these cases were 15 more for paralytic and 10 fewer for non-paralytic cases than in the preceding week. The largest returns were in Lancashire 19 (Manchester C.B. 3, Blackpool C.B. 2, Padiham U.D. 2, Burnley R.D. 2); Yorkshire West Riding 11 (Leeds C.B. 4, Bradford C.B. 3, Ripon M.B. 2); London 6 (Fulham 2, Islington 2).

The largest returns for dysentery were Yorkshire West Riding 113 (Huddersfield C.B. 43, Dearne U.D. 28, Huddersfield C.B. 11, Mexborough U.D. 10), London 61 (Islington 17, Battersea 12), Glamorganshire 55 (Rhondda M.B. 23, Barry M.B. 19), Lancashire 47 (Liverpool C.B. 23), and Warwickshire 36 (Coventry C.B. 28).

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 18** (No. 42) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	10	6	2	0	3	1	0	2	0	1
Dysentery	658	73	170	9	3	175	14	118	8	7
Encephalitis, acute	2	0		0		3	1		1	
Enteric fever:										
Typhoid ..	4	1	0	0	1	2	0	0	0	
Paratyphoid ..	6	1	0	0		7	0	0	0	
Food-poisoning ..	259	35	24	1		90	17	57	2	
Infective enteritis or diarrhoea under 2 years				11	34				6	36
Measles*	3,739	198	38	12	139	1,310	27	19	105	12
Meningococcal infection	14	2	7	0		31	1	10	0	1
Ophthalmia neonatorum	19	3	9	0		26	4	3	0	
Pneumonia† ..	251	18	144	3		2,280	147	957	32	20
Poliomyelitis, acute:										
Paralytic ..	47	6	12	1	7	64	3	2	4	4
Non-paralytic ..	23	1				16	2			
Puerperal fever§ ..	215	36	16	0		307	40	7	3	1
Scarlet fever ..	795	70	117	20	27	382	29	34	20	30
Tuberculosis:										
Respiratory ..	507	70	68	17		529	70	107	16	
Non-respiratory	74	5	14	7		57	5	8	2	
Whooping-cough ..	476	15	83	49	32	318	20	29	1	14

DEATHS	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery	1	1		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	2	0	0	0			0	0	0	0
Infective enteritis or diarrhoea under 2 years	8	0	1	0	0		0	0	0	1
Influenza	6	1	0	0	0		66	39	26	6
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0	0	
Pneumonia ..	345	23	15	14	4		77	61	32	6
Poliomyelitis, acute	6	0	1	0	0		0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	67	6	3	0	3		4	5	2	2
Non-respiratory		1	0	1	0		0	0	1	0
Whooping-cough ..	0	0	0	0	0		0	0	0	0
Deaths 0–1 year ..	255	21	30	6	8		31	26	7	8
Deaths (excluding stillbirths) ..	8,630	692	543	95	161		958	694	168	154
LIVE BIRTHS ..	14,208	1182	1092	221	405		1147	1041	212	417
STILLBIRTHS ..	271	20	24				28	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

P.R.F.P.S.—Mr. A. H. JACOBS, surgeon-in-charge of the urological department at Glasgow Royal Infirmary, was elected president of the Royal Faculty of Physicians and Surgeons of Glasgow at the annual meeting on November 3. He succeeds Professor STANLEY ALSTEAD.

Royal College of Physicians.—At the quarterly comitia held on October 30, with the president, Professor ROBERT PLATT, in the chair, it was announced that THE QUEEN had accepted the invitation to become Visitor to the College. The following were elected councillors of the College: Dr. W. D. W. BROOKS, Dr. M. I. A. HUNTER, Dr. G. E. GODBER, and Dr. W. H. MCMENEMEY. Dr. C. E. NEWMAN was elected to the committee of management of the Conjoint Board. Professor R. PLATT, Sir HAROLD BOLDERO, Dr. R. R. BOMFORD, Dr. G. W. HAYWARD, and Dr. S. R. F. WHITTAKER were elected to the standing joint committee of the three Royal Colleges. The appointment of Dr. L. G. NORMAN as Milroy lecturer for 1960 was announced: his subject would be "The Medical Aspects of the Prevention of Road Accidents." The award of the Gilbert Blane medal to Surgeon Commander W. E. CROCKER, R.N., was announced.

M.R.C.P.—The following, having satisfied the censors' board, were elected Members of the Royal College of Physicians of London:

H. B. Anstall, N. A. Beardwell, D. R. Bell, P. Blackledge, J. H. Briggs, W. C. Cockburn, J. E. Cooper, M. A. Cowan, S. G. Elkington, M. G. Gelder, H. B. Griffith, J. H. Highman, J. R. Hobbs, A. D. Isaacs, Y. K. Lee, W. A. Lishman, M. S. Losowsky, P. E. S. Loubser, T. McKendrick, P. Markman, R. D. Montgomery, P. D. Mulcahy, S. Naimi, K. R. Norton, R. D. G. Peachey, S. Posen, D. D. Reid, P. A. Russell, E. A. Ryan, J. Schneider, D. G. Smith, J. R. Smythies, G. M. Stern, D. W. Sumner, J. R. Tighe, A. E. P. Twort, P. G. Wallis, M. F. R. Waters, D. J. Weatherall, D. N. Whitmore, and F. W. Wright.

Department of Virology, Glasgow.—We reproduce here the architect's drawing for the building of the new department of virology at Glasgow University, of which Professor M. P. G. STOKER was recently appointed as its first head (*Journal*, April 26, p. 1013). This is stated to be the first university department to be devoted solely to the study of

viruses. The institute, designed by Messrs. Basil Spence and Partners, will be at the intersection of Church Street and Moy Street, Glasgow, and is expected to be finished in 1960. The cost is being met from a £225,000 grant from the Scottish Hospital Endowments Research Trust. The institute, besides providing for the department's teaching and research on viruses and virus diseases, will also house a Medical Research Council unit and part of the university department of genetics. The building will be sealed and have a full plenum system of ventilation to facilitate sterility. The basement will be equipped with an electron microscope, dark-rooms, and instrument workshops. On the ground floor there will be an animal block, media and glass-washing rooms, etc. The first and second floors will

provide biochemical and other laboratories, including facilities for chromatography, cytology, and work with radioisotopes, and a classroom. On the top floor there will be a library, offices, and rooms for quiet study.

Gairdner Foundation Awards.—Among the seven recipients of the Gairdner Foundation's first international awards for work on arthritis and heart diseases are Professor W. D. M. PATON (Royal College of Surgeons) and Professor ELEANOR ZAIMIS (Royal Free Hospital). They receive an award of $5,000 for their discovery of the methonium compounds, "the first drugs to be proven practical and effective in treatment of high blood pressure." The Foundation's award of merit (a prize of $25,000) is shared between Dr. ALFRED BLALOCK and Dr. HELEN B. TAUSSIG (Johns Hopkins University) for their contributions to cardiac surgery. Other awards of $5,000 go to Drs. H. M. ROSE and C. RAGAN (New York) for their laboratory test for rheumatoid arthritis, and to Dr. W. G. BIGELOW (Toronto) for his use of hypothermia in cardiac operations. The awards will be presented next May in Toronto, the home city of the Gairdner Foundation.

Human Relations in Industry.—The joint M.R.C.–D.S.I.R. committee on human relations in industry has issued its final report (H.M.S.O., London, price 3s. net). In it the committee reviews the research it has sponsored and indicates the lessons that may be drawn from its experience. Published under the same cover as the "final report" is the report of the joint committee on individual efficiency in industry. This committee, under the chairmanship of Sir FREDERIC BARTLETT, F.R.S., was appointed in 1953 to advise on research in this field.

Norman McAlister Gregg Prize.—The Ophthalmological Society of New South Wales announces that the Norman McAlister Gregg Prize will be awarded in 1959. The prize, which consists of 100 guineas and a bronze medallion, will be awarded to the British subject whose submitted original work, on any subject, is deemed to be the most valuable contribution to knowledge of ophthalmology. Intending candidates should notify Dr. JOHN HORNBROOK, 147, Macquarie Street, Sydney, at least two months before the closing date, which is October 31, 1959.

Christmas Seals.—N.A.P.T. and the National Spastics Society are selling Christmas seals this year. The National Association for the Prevention of Tuberculosis and Diseases of the Chest and Heart offers seals in sheets of 100 different designs illustrating familiar British flowers, price 4s. for 100. The seals are obtainable from Tavistock House North, Tavistock Square, London, W.C.1. The National Spastics Society offers sets of 120 seals in 12 designs, asking 1d. a seal. The seals are obtainable from 28, Fitzroy Square, London, W.1.

Sheffield University.—Dr. M. W. PARTINGTON has been appointed a temporary lecturer in child health. The University also announces a grant of $8,000 from the Rockefeller Foundation to the department of biochemistry. This will enable the department to buy a refrigerated centrifuge.

London University.—The title of reader in biology in the University of London has been conferred on Dr. H. KALMUS in respect of his post at University College.

U.S. Air Force Surgeon General.—Major-General OLIVER K. NIESS will succeed Major-General DAN C. OGLE as surgeon general of the United States Air Force on December 1.

Sir Harry Platt left on October 30 for a lecture tour in India, Pakistan, and Ceylon arranged by the British Council. He expects to be back early in January.

"Family Doctor."—The November issue includes articles on sleep by Drs. F. R. C. Casson and W. H. S. Wallace, winter clothes by Dr. O. G. Edholm, and the common cold by Dr. K. C. Hutchin. There is also a description of the endocrine glands.

COMING EVENTS

London Medical Exhibition.—At the New Hall of the Royal Horticultural Society, Greycoat Street, Westminster, London, S.W.1, November 10–14 (11 a.m.–6.30 p.m.; on November 13 the time of closing is 7.30 p.m.).

Allergic Disorders.—The British Society for Immunology and the British Association of Allergists will hold a joint symposium on "Immunological Aspects of Allergic Disorders" at the Wellcome Building, Euston Road, on November 14 and 15. Further details from Dr. R. G. WHITE, London Hospital, London, E.1.

Fellowship for Freedom in Medicine.—Annual general and extraordinary general meetings will be held at Caxton Hall, Westminster, at 2 p.m. on November 15.

Charles West Lecture.—Dr. E. MILDRED CREAK will lecture on "Child Health and Child Psychiatry—Neighbour or Colleagues?" on November 18, at 5 p.m., at the Royal College of Physicians, Pall Mall East.

Faculty of Radiologists.—Fourth Crookshank Lecture on "The Contribution of *X* Rays to the Basic Medical Sciences" will be given by Lord COHEN OF BIRKENHEAD on November 21, at 5 p.m., at the Royal College of Surgeons, Lincoln's Inn Fields.

College of General Practitioners.—Symposium on Dyspepsia, November 23, at 10 a.m.–4 p.m. at the Wellcome Building, Euston Road, London, N.W.1.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Archives of Disease in Childhood.—Issued six times a year (£4 4s. annually). The new issue, Vol. 33, No. 171, includes:

SEVERE INFANTILE HYPERCALCAEMIA, WITH SPECIAL REFERENCE TO THE FACIES. M. C. Joseph and D. Parrott.
CONGENITAL ABSENCE OF THE INTRAHEPATIC BILE DUCTS. Leonard Haas and Richard H. Dobbs.
REPLACEMENT TRANSFUSION AS A MEANS OF PREVENTING KERNICTERUS OF PREMATURITY. V. Mary Crosse, Patricia G. Wallis, and Anna M. Walsh.
SERUM TRANSAMINASE VARIATIONS IN CHILDHOOD. Paolo Tolentino and Marcella Rossi.
A TEST FOR COELIAC DISEASE. W. W. Payne and V. Jenkinson.
A LONGITUDINAL STUDY OF THE GROWTH AND DEVELOPMENT OF PREMATURELY AND MATURELY BORN CHILDREN.
PART I. INTRODUCTION. Cecil Mary Drillien.
PART II. PHYSICAL DEVELOPMENT. Cecil Mary Drillien.
PANCREATITIS IN YOUNG CHILDREN. J. Collins.
HERPES ZOSTER OPHTHALMICUS IN CHILDREN. S. M. Tucker.
OBSERVATIONS ON THE BROMIDE PARTITION TEST IN THE DIAGNOSIS OF NON-PURULENT MENINGITIS. V. S. Nicol and H. T. Fawns.
PNEUMATOSIS INTESTINALIS IN CHINESE CHILDREN. C. S. Muir.
PHYSICAL DEVELOPMENT OF SCHOOLGIRLS IN UPPER BURMA. C. V. Foll.
THE PREVALENCE OF DENTAL CARIES IN RELATION TO MATURITY. J. N. Mansbridge.
FAMILIAL DYSAUTONOMIA. T. McKendrick.
AUTOPSY FINDINGS IN A CASE OF PITUITARY DWARFISM. A. T. Sandison.
INSUFFICIENT GLUCURONIDE FORMATION IN THE NEWBORN AND ITS RELATIONSHIP TO THE PATHOGENESIS OF ICTERUS NEONATORUM. M. Vest.
THE FIRST ARCH SYNDROME. J. McKenzie.

British Journal of Industrial Medicine.—Issued four times a year (£3 annually). The new issue (Vol. 15, No. 4) includes:

CANCER OF THE LUNG AND NOSE IN NICKEL WORKERS. Richard Doll.
SOME OBSERVATIONS ON THE INCIDENCE OF RESPIRATORY CANCER IN NICKEL WORKERS. J. Gwynne Morgan.
THE PATHOLOGY OF THE LUNGS IN FIVE NICKEL WORKERS. W. Jones Williams.
CHRONIC CHLOROFORM INTOXICATION. P. J. R. Challen, D. E. Hickish, and Joan Bedford.
COUNTING ERRORS DUE TO OVERLAPPING PARTICLES IN THERMAL PRECIPITATOR SAMPLES. S. A. Roach.
RESPIRATORY FUNCTION OF WITWATERSRAND GOLD-MINERS. Saul Zwi and Margaret R. Becklake.
A STATISTICAL STUDY OF COAL-MINING ACCIDENTS. F. D. K. Liddell and Joan May.
ASEPTIC NECROSIS OF BONE IN CAISSON DISEASE. John D. Thomson and Andrew B. Young.
SOME NOTES ON THE EFFECTS OF EXCESSIVE NOISE ON THE HEARING OF A GROUP OF WORKERS. G. F. Keatinge and S. Laner.
AN INVESTIGATION OF SOME HEALTH HAZARDS IN AN INERT-GAS TUNGSTEN-ARC WELDING-SHOP. P. J. R. Challen, D. E. Hickish, and Joan Bedford.
THE ESTIMATION OF GASEOUS ACID IN DOMESTIC PREMISES. J. J. Phair R. J. Shephard, G. C. R. Carey, and M. L. Thomson.
QUARRY BANK MILL: I. THE STORY OF THE MILL. Robert Murray.

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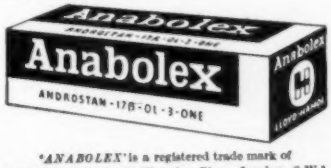

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SOCIETIES AND LECTURES

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Monday, November 10

GUY'S HOSPITAL.—At Anatomy Lecture Theatre, 5.15 p.m., lecture-demonstration in endocrinology by Dr. P. M. F. Bishop: Hypothyroidism. Guest speaker, Professor D. Hubble.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Guest lecture by Miss G. Hill: Menorrhagia.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Psychiatric Aspects of Organic Cerebral Disease.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., Dr. J. R. Postgate: Sulphur Bacteria—Reductive Stages of the Bacterial Sulphur Cycle.

Tuesday, November 11

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. Edward Glover: Psycho-analysis and Modern Social Medicine.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. F. Borrie: Circulatory and Vascular Reactions.

MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Clinical Sciences Building, York Place, 7.30 for 8 p.m., Dr. J. K. Steward: Tumours in Childhood.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—4 p.m., Blackham Lecture, 1958, by Brigadier Sir John Boyd, KL., F.R.S.: Yellow Fever and its Prevention. (Illustrated.)

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, 5 p.m., Dr. H. D. Attwood: Investigation of Pulmonary Embolism.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Dr. George Crosby: Gynaecology in General Practice.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., Professor J. F. Danielli, F.R.S.: Generalized Cell Theory and its Relevance to Certain Problems of Drug Action.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. A. D. Gordon: Neuroradiological Investigations.

Wednesday, November 12

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. A. Dudgeon: Virus Diseases.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. A. M. C. Macpherson: Some Chest Diseases in Childhood.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. J. D. Fergusson: Prostatic Cancer.

MANCHESTER MEDICAL SOCIETY.—At Physiology Theatre, Manchester University, 4.30 for 5 p.m., Dr. A. F. Rogers: A Doctor in Antarctica.

●NATIONAL COLLEGE OF RUBBER TECHNOLOGY, Northern Polytechnic, Holloway Road, N.—6.30 p.m., Professor C. G. Rob: Synthetic Materials in Vascular Surgery.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Guest Lecture by Professor C. H. Gray: Role of the Endocrine Organs in Diabetes Mellitus.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Weild Lecture by Professor D. W. Smithers: On the Pathogenesis of Cancer.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mr. H. Beric Wright: Environmental Medicine in Industry.

Thursday, November 13

HONEYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Professor G. I. Scott: Optic Nerves.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m. Robert Jones Lecture by Mr. Norman Capener: Spondylolisthesis: Spinal Strain.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION: PSYCHOTHERAPY AND SOCIAL PSYCHIATRY SECTION.—At 11, Chandos Street, Cavendish Square, W., 8 p.m., Dr. E. B. Strauss: Value of Narcoanalysis in Psychiatric Practice. Dr. W. A. H. Stevenson and Dr. R. A. Sandison will take part in the discussion.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION.—At Royal Society of Medicine, 2.15 p.m., Maudsley Lecture by Dr. Leo Kanner (Baltimore): Trends in Child Psychiatry.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, 5 p.m., Professor H. Grüneberg, F.R.S.: Causes of Congenital Defects.

Friday, November 14

BIOCHEMICAL SOCIETY.—At National Institute of Medical Research, Ridgeway, Mill Hill, N.W., 2 p.m., 377th meeting.

HILL END HOSPITAL CLINICAL SOCIETY.—At Hill End Hospital, St. Albans, 8.30 p.m., talk by Dr. R. Robertson. Members of Mid-Herts Division, B.M.A., are invited.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. S. C. Gold: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. E. H. Hudson: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—4.30 p.m., Annual Address by T. G. Wilson: Modern Treatment of Deafness in Historical Perspective.

PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., joint meeting with Plymouth Division, B.M.A. Mr. T. Holmes Sellors: Thoracic Surgery.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Guest lecture by Professor W. C. Wilson: Ins and Outs of Surgical Practice. (2) 4 p.m., Guest lecture by Professor W. M. Arnott: Regional Distribution of Blood Flow in Low Output Syndromes.

Saturday, November 15

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Children's Department, Farnborough Hospital, Kent, 3 p.m., Dr. Peter Scott: Crime and Adolescence.

Sunday, November 16

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE AND NORTH-WEST ENGLAND FACULTY, COLLEGE OF GENERAL PRACTITIONERS.—At Theatre 1, Clinical Sciences Building, York Place, 11 a.m., Mr. Gordon Jack and Dr. F. W. A. Turnbull: Influence of Modern Advances on One's Approach to Chest Disease.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—T. L. Pilkington, M.R.C.S., L.R.C.P., D.P.M., Whole-time Consultant Psychiatrist and Deputy Medical Superintendent to Lea Colony, Bromsgrove, and Lea Castle Colony, Kidderminster; N. K. Shinton, M.B., Ch.B., M.R.C.P., Whole-time Consultant Pathologist to the Coventry Group of Hospitals; W. N. Boyd, M.B., Ch.B., F.R.C.S.Ed., D.M.R.D., Part-time Consultant Radiologist to the Stoke-on-Trent Group of Hospitals; J. A. Litchfield, M.D., M.R.C.P., Part-time Consultant Physician (Geriatrics) to the Mid-Worcestershire Group of Hospitals; A. V. Jenkins, M.B., B.S., F.F.A. R.C.S., Whole-time Consultant Anaesthetist to Birmingham (Selly Oak) group of hospitals; W. Sewell, F.R.C.S., Part-time Consultant Surgeon (seven notional half-days weekly) to Stoke-on-Trent group of hospitals; H. S. Trafford, M.B., Ch.B., F.R.C.S.Ed., D.Obst.R.C.O.G., Whole-time Consultant Surgeon to Stoke-on-Trent group of hospitals.

FREED, LOUIS F., M.A., M.D., D.Phil., D.P.M., F.R.S.S.Afr., of Johannesburg, South African Editor of *Vita Humana*, international journal of human development. Dr. Freed is lecturer in the Department of Psychiatry of the University of the Witwatersrand.

FRIZELLE, G. M., T.D., M.D., D.P.H., Medical Officer of Health, East Hertfordshire Combined Districts.

GATHERER, ALEXANDER, M.B., Ch.B., D.P.H., Deputy Medical Officer of Health and Deputy Principal School Medical Officer to the County Borough of Warrington.

HOARE, E. D., M.D., Director of Department of Clinical Pathology at the London Clinic.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—Marion V. Miles, M.R.C.S., L.R.C.P., D.C.H., House-physician; E. J. Guthrie, M.B., B.Ch., House-surgeon to Orthopaedic and Plastic Departments; D. Y. Mackenzie, M.D., M.R.C.P., D.C.H., Registrar to Department of Physical Medicine; W. P. Kennedy, M.D., D.C.H., Assistant Medical Registrar; Doreen A. Birch, M.B., Ch.B., F.R.C.S.Ed., Registrar to Ear, Nose, and Throat Department; D. E. Sturdy, M.B., B.S., F.R.C.S., Surgical Registrar; Alice E. M. Van Waterschoodt, M.B., B.S., D.Obst.R.C.O.G., D.A., Junior Anaesthetic Registrar.

LIVERPOOL REGIONAL HOSPITAL BOARD.—J. K. Wilson, M.D., M.R.C.O.G., D.Obst.R.C.O.G., Part-time Consultant Obstetrician and Gynaecologist for two sessions per week at Ormskirk County Hospital; A. S. Woodcock, M.D., Consultant Pathologist (whole-time or maximum part-time sessions) at Whiston and Rainhill Hospitals; H. E. Parry, M.B., B.S., M.R.C.P., D.C.H., Whole-time Consultant Physician and Deputy Medical Superintendent (Resident) at Fazakerley Hospital; P. B. O'Neill, M.B., B.S., F.R.C.S., D.L.O., Part-time Consultant Otorhinolaryngologist for seven sessions for St. Helens, Warrington, Ormskirk, and Runcorn areas; W. M. Owen, M.B., B.S., F.R.C.S., D.L.O., Part-time Consultant Otorhinolaryngologist for five sessions at Clatterbridge and Wirral Hospitals; J. Siegler, M.B., B.S., F.R.C.S., D.L.O., Assistant Consultant Otorhinolaryngologist for two sessions at Bootle, Walton, and John Bagot Hospitals; C. M. Ogilvie, M.D., M.R.C.P., Part-time Consultant Physician for four sessions in the Regional Thoracic Surgery Unit at Broadgreen Hospital; E. Walker, M.D., D.P.H., D.M.R.D., Part-time Consultant Radiologist for four sessions at Sefton General Hospital; I. M. Cuthill, M.B., Ch.B., M.R.C.P.Ed., Whole-time Assistant Chest Physician in the Chester and District area.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Durber.—On September 16, 1958, at the City General Hospital, Stoke-upon-Trent, Staffs, to Phyllis (formerly Walton), wife of Dr. C. E. Durber, a sister for Peter and David—Penelope Joy.

Mitchell.—On October 26, 1958, at Scunthorpe Maternity Home, to Drs. W. P. and Jane (formerly Higson) Mitchell, of High Street, Belton, Doncaster, Yorks, a son.

O'Kelly.—On October 10, 1958, at Farnborough, Hants, to Dorothy Mary, S.R.N., S.C.M., wife of Captain Frank O'Kelly, R.A.M.C., a brother for Margaret and Julie.

DEATHS

Chapman.—On October 16, 1958, at Hastings, Sussex, Donald Poyntz Chapman, M.R.C.S., L.R.C.P., of Wingarth, Tydehams, Newbury, Berks, Surgeon Commander, R.N. (retired), aged 82.

Dobson.—On October 12, 1958, at The House, Wrightington Hospital, Appley Bridge, near Wigan, Lancs, Jonathan Dobson, F.R.C.S., aged 51.

Druitt.—On October 12, 1958, Daniel Cuthbert Druitt, M.R.C.S., L.R.C.P., of Gleneagles, Petworth, Sussex, aged 74.

Fraser.—On October 14, 1958, in a nursing-home, Bournemouth, Hants, Sarah Louise Fraser, M.B.E., M.D., late of York, aged 84.

Fridjohn.—On October 14, 1958, at Ellaston, Ham Common, Richmond, Surrey, Maurice Henry Fridjohn, M.D., aged 54.

Hill.—On October 8, 1958, at Rosedene, 56, Buckingham Way, Wallington, Surrey, Robert McCowan Hill, D.S.O., M.B., Ch.B., aged 75.

Julian.—On August 19, 1958, Frederick Bennett Julian, *M.C.*, M.B., B.Ch., M.Sc., of Hatton House, Mather Avenue, Liverpool, aged 65.

Lamont.—On September 3, 1958, at Seaton, Devon, Charles Antony Lamont (formerly Lavery), M.B., Ch.B., F.R.F.P.S., late Squadron Leader, R.C.A.F.

Lewin.—On October 16, 1958, at Mole Cottage, Great Molewood, Hertford, George Lewin, M.B., B.S., late of 1, Haling Park Road, South Croydon, aged 82.

Mackenna.—On October 16, 1958, at Mansion House Road, Paisley, John George Mackenna, M.B., Ch.B., D.P.H.

Miller.—On October 11, 1958, at 34, Clarewood Court, London, W., Arthur Alfonce Miller, F.R.C.S.Ed., D.L.O., of 20, Harley Street, London, W.

Ockwell.—On October 17, 1958, at Guy's Hospital, London, E.C., Charles Melton Ockwell, M.D., F.R.C.S., D.P.H., of The Coppice, Pilgrim's Way, Kemsing, Kent, aged 74.

Paterson.—On October 2, 1958, at 140, Mugdock Road, Milngavie, Glasgow, Robert Lamb Paterson, M.B., Ch.B., D.P.H., late of Sulenkama, South Africa.

Popham.—On October 9, 1958, Cyril Popham, O.B.E., L.R.C.P.&S.I., L.R.F.P.S., Colonel, late R.A.M.C., of Centre Oak, Blackwater, Camberley, Surrey.

Wakefield.—On October 4, 1958, at Birklands, Kendal, Westmorland, Roger William Wakefield, M.B., B.Ch., J.P., aged 92.

Widdup.—On October 6, 1958, in Australia, Alec Harley Widdup, M.B., B.Chir., formerly of Thornton-in-Craven, Skipton, Yorks.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

P.A.S. and Pulmonary Tuberculosis

Q.—*Is calcium B-P.A.S. as effective in the treatment of pulmonary tuberculosis as sodium P.A.S.?*

A.—The most important effect of P.A.S. and its analogues in the treatment of pulmonary tuberculosis consists in its ability, when given in combination with streptomycin or isoniazid, to diminish the liability to the emergence of strains of tubercle bacilli resistant to the other drugs. The therapeutic effect of P.A.S. alone is considerably less than that of the other two commonly used drugs. There is good evidence that tolerable doses of sodium P.A.S. are effective in this respect.[1,2] The best way of estimating the effectiveness of any alternative preparation to the sodium salt of P.A.S. is therefore to determine whether, when given in combination with streptomycin or isoniazid to patients whose organisms are known to be sensitive to the drugs used, it prevents the emergence of drug-resistant organisms. Evidence on this point is difficult to obtain, but Lewis[3] has reported 39 patients who were admitted to hospital with pulmonary tuberculosis and were treated with calcium benzamidosalicylate (Ca B-P.A.S.) with streptomycin or isoniazid for a period of at least two months. Of these, at least 20 subsequently produced tubercle bacilli with impaired sensitivity to one or more of the standard drugs. Since some of these patients had been treated as out-patients, it was possible that not all of them had taken the prescribed drugs conscientiously, and drug sensitivity tests had not been done in most of them before treatment was begun. However, seven of them were known to have taken the drugs conscientiously and to have had sensitive organisms before Ca B-P.A.S. was given. In three of these bacilli resistant to isoniazid or streptomycin emerged, and in two more sputum remained positive after six or eight months of treatment, although sensitivity tests were not done. These results indicate that, in the commonly used dose of 14 g. a day, Ca B-P.A.S. is ineffective in preventing the emergence of organisms resistant to streptomycin or isoniazid. Undissociated B-P.A.S. is very much less active than P.A.S.[4] and its therapeutic activity therefore depends upon its conversion to P.A.S. Lewis points out that, assuming complete hydrolysis of Ca B-P.A.S. and with the knowledge that only about 60% of an oral dose is absorbed from the gut, the dose of Ca B-P.A.S. which would correspond with the dose of sodium P.A.S. known to be effective in preventing emergence of resistance to streptomycin is no less than 48 g. daily. This is far above the customarily used dose, and it is doubtful if it would be tolerated any better than the normal dose of sodium P.A.S.

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1 Medical Research Council, *Brit. med. J.*, 1953, **2**, 1005.
2 —— ibid., 1955, **1**, 435.
3 Lewis, D. O., *Tubercle (Lond.)*, 1958, **39**, 247.
4 Schönholzer, G., Lauener, H., and Hurni, H., *Schweiz. med. Wschr.*, 1955, **85**, 222.

Oedema in Pre-eclampsia

Q.—*Is it necessary to restrict the fluid intake in the control of oedema in pre-eclampsia?*

A.—The best method of controlling the oedema of pre-eclampsia remains in doubt. Indeed, it is not established that the control of oedema *per se* by any method is of value. It is, nevertheless, usually attempted.

If the oedema is associated with sodium retention, as is generally believed to be the case in pre-eclampsia, the complete elimination of sodium from the diet is theoretically all that is necessary. In fact, however, a sodium-free diet is impracticable. It is therefore usual to compromise by restricting both sodium and fluid. The avoidance of fluid to the extent of causing dehydration could be harmful and even result in uraemia. This is unlikely to happen in a waterlogged patient, in whom experience shows it to be safe to reduce the intake of fluid to 20 oz. (0.6 l.) in 24 hours. Moreover, no harm can result when the amount of fluid allowed is related to the output of urine, this being the usual clinical guide. The recently introduced orally administered saluretics (e.g., acetazolamide and chlorothiazide), unlike the older mercurial diuretics given by injection, do control the oedema of toxaemia. Chlorothiazide acts by increasing chloride excretion and this in turn raises the sodium output. It also has a less important action as a carbonic anhydrase inhibiting factor. This new drug is therefore being used without restricting the patient's intake of either fluid or sodium. However, in the presence of liver damage (and especially if the sodium intake is restricted) chlorothiazide can produce dangerous hypokalaemia.[1] There is, therefore, some reason to question the advisability of using this drug in the treatment of pregnancy toxaemia unless the patient is having potassium supplements and is in a hospital, where the electrolyte balance can be constantly controlled. Even then its value is doubtful. Although it may improve maternal oedema it does not—as judged by foetal survival rates—benefit significantly the underlying disease.[2]

There is at present probably no better method of controlling the oedema of pre-eclampsia than by physical rest (which is indicated on other grounds and which in itself promotes elimination of fluid), by reasonable restriction of the intake of fluid and sodium, and possibly by administering a simple sodium replacement diuretic such as ammonium chloride.

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1 Read, A. E., Haslam, R. D., Laidlaw, J., and Sherlock, S., *Brit. med. J.*, 1958, **1**, 963.
2 Bayliss, R. I. S., *Practitioner*, 1958, **181**, 216.

Treatment of Rabies

Q.—*Where may supplies of rabies vaccine and serum be obtained in England and Wales?*

A.—A Ministry of Health memorandum (H.M.(58)66), August, 1958, lists the following centres as holding supplies of rabies vaccine (for active immunization) and serum (for immediate passive protection) for the treatment of rabies.

London.—Central Public Health Laboratory, Colindale Avenue, N.W.9 (Colindale 7041).

Newcastle.—Public Health Laboratory, or Institute of Pathology, General Hospital, Westgate Road, Newcastle, 4 (Newcastle 38811).

Liverpool.—Public Health Laboratory, 126, Mount Pleasant, Liverpool (Royal 3636).

Wales.—Public Health Laboratory, Institute of Preventive Medicine, The Parade, Cardiff (Cardiff 29110 and 23967).

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